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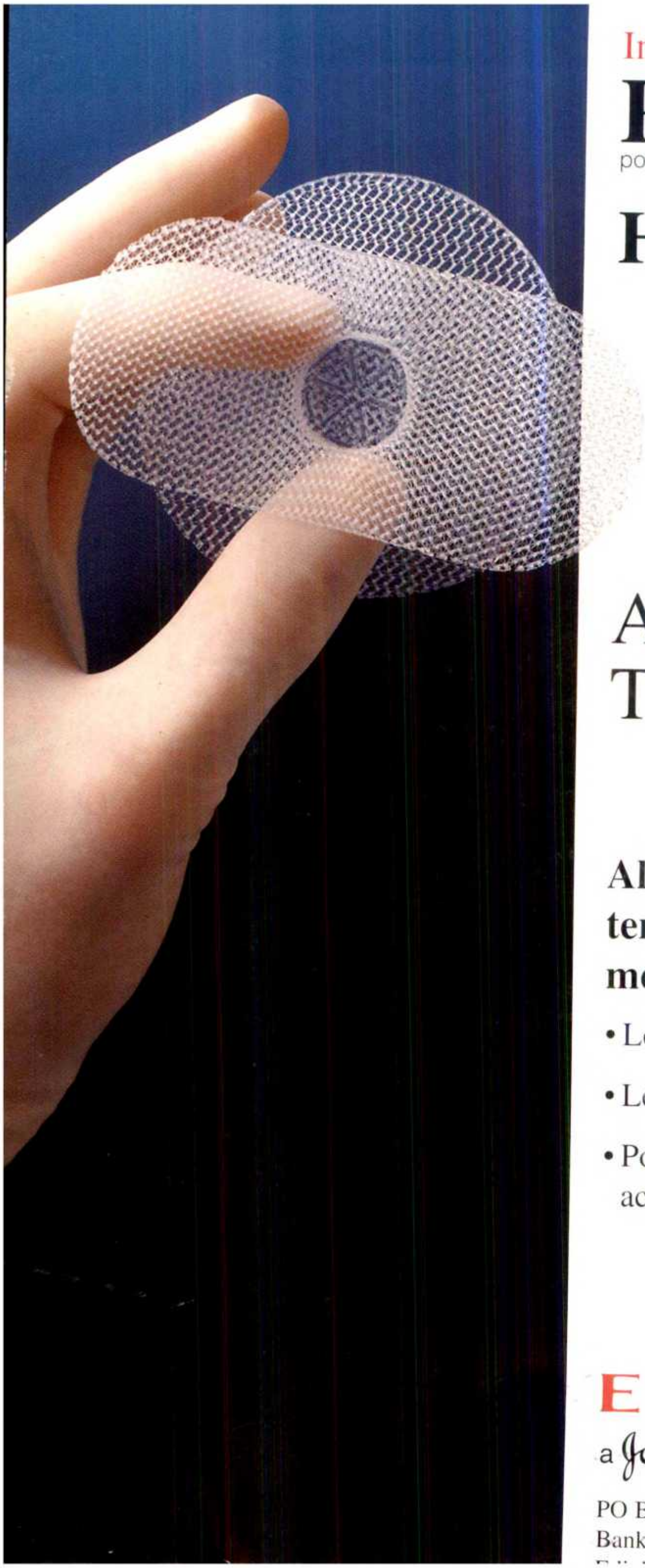

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The *British Journal of Surgery* features the very best in clinical and laboratory-based research on all aspects of general surgery and related topics. Developing areas such as minimally invasive therapy and interventional radiology are strongly represented.

The inclusion of Leading Articles, Reviews, Original Articles, and articles 'For Debate' means that the *British Journal of Surgery* offers an appropriate format for any length or type of submission; in addition, there are abstracts from key meetings, correspondence, book reviews and regular digests by the European Editor of the contents of other major journals. The *British Journal of Surgery* will be of interest not only to general surgeons, but also to specialty surgeons and those working in related fields.

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This annual international colorectal course in Fort Lauderdale has been for the last several years, one of the largest postgraduate colorectal courses in the world. The 9th Annual Symposium attracted almost 1000 registrants from 61 foreign countries. This 10th Anniversary course is carefully balanced to include three intensive days of lectures by the world's leading experts. Topics primarily encompass challenges, controversies and complications. Examples include panels in "Controversies in Ulcerative Colitis Surgery", "Frustrating Fistulas", Treating Complications", " Re-operative Surgery (What Happens When Your Initial Treatment Fails?)", and "Challenges and Conundrums". Four additional areas that will be analyzed in great detail include colorectal neoplasia, inflammatory bowel disease, colorectal physiology, and technical aspects of surgery. This last facet will be depicted by a compilation of expertly produced videos on a wide array of interesting subjects. There will be ample time for answering questions and for discussion with all of the experts during the six hours of panel discussion and the addition of the "Provoke the Professor" breakfasts and "Expert Exchange" lunch tables.

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The Deadline for the submission of Abstracts to the Scientific Secretariat has been set to: December 13, 1998

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Tom Benson, Teacher's Pet

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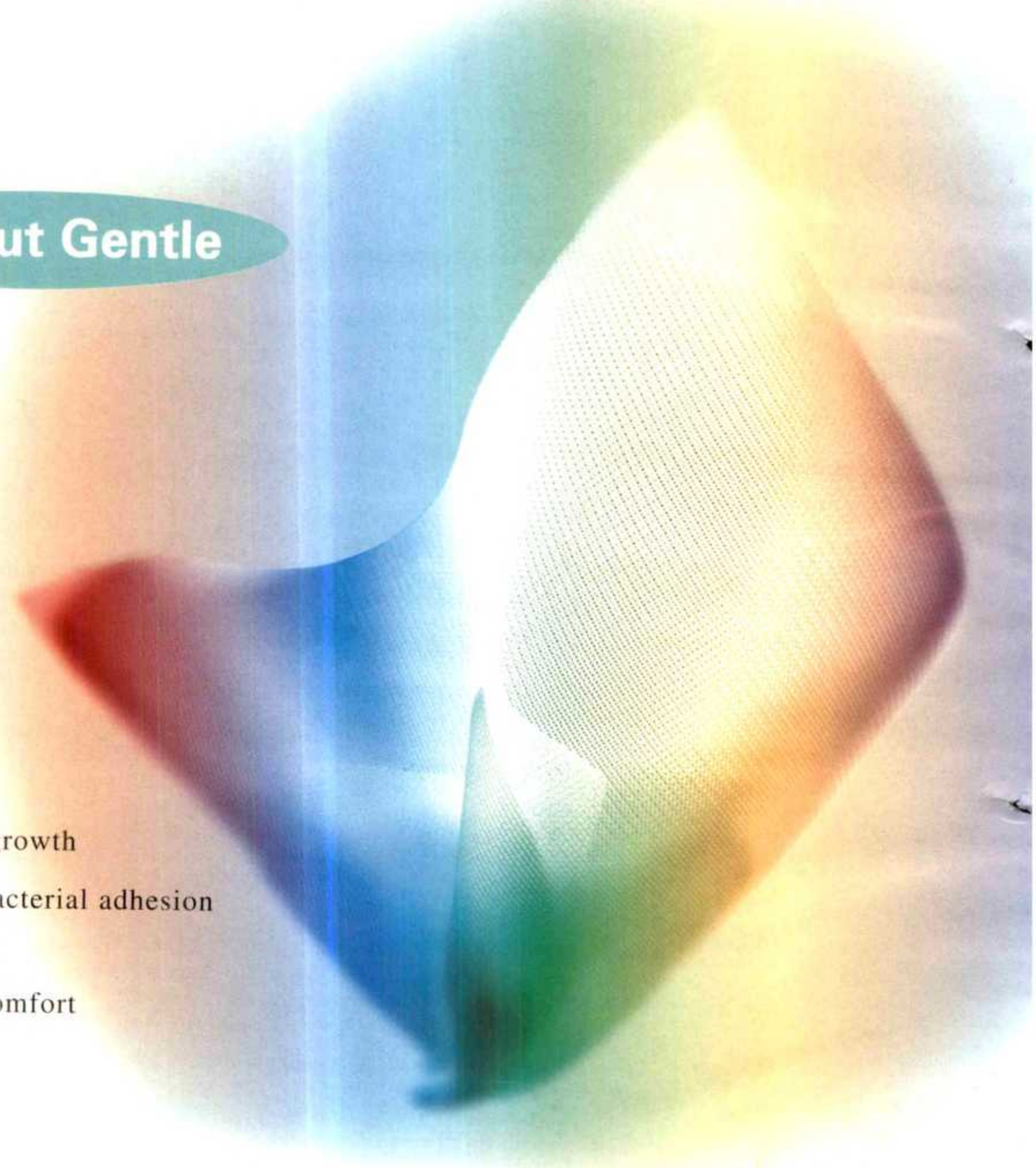

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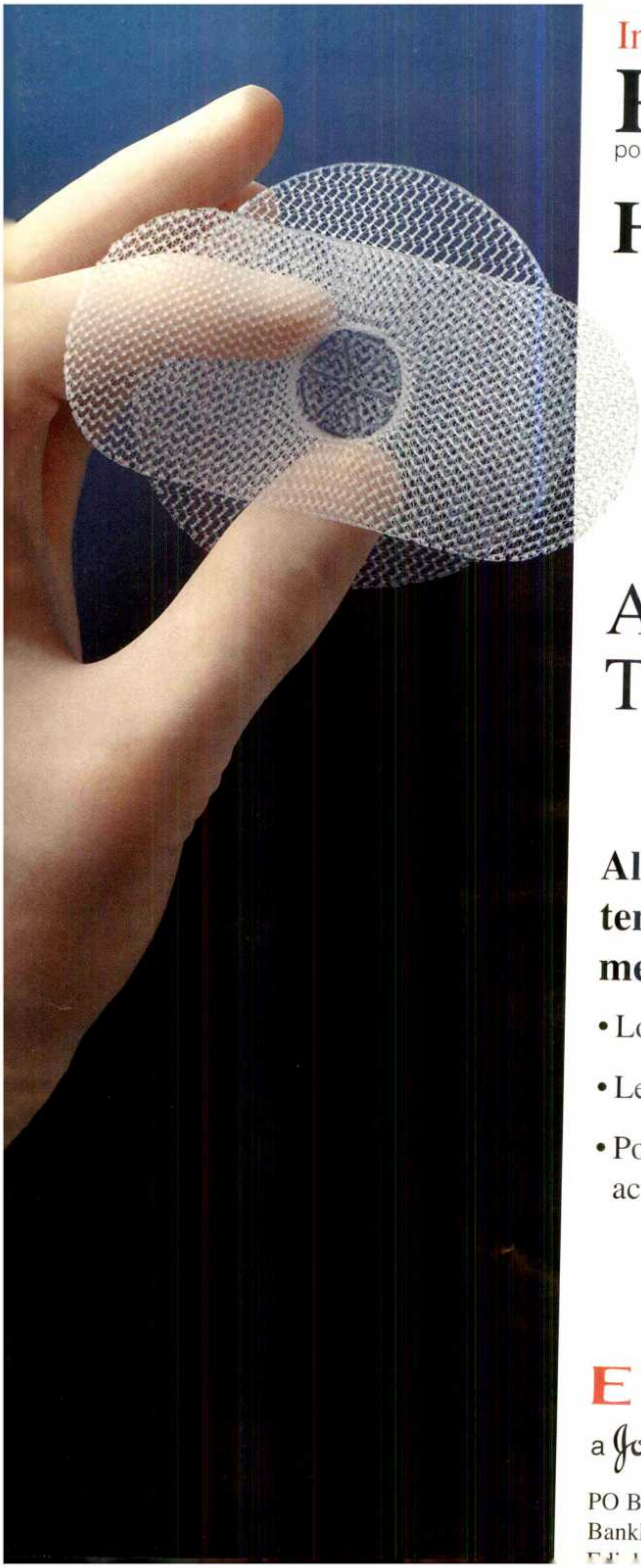

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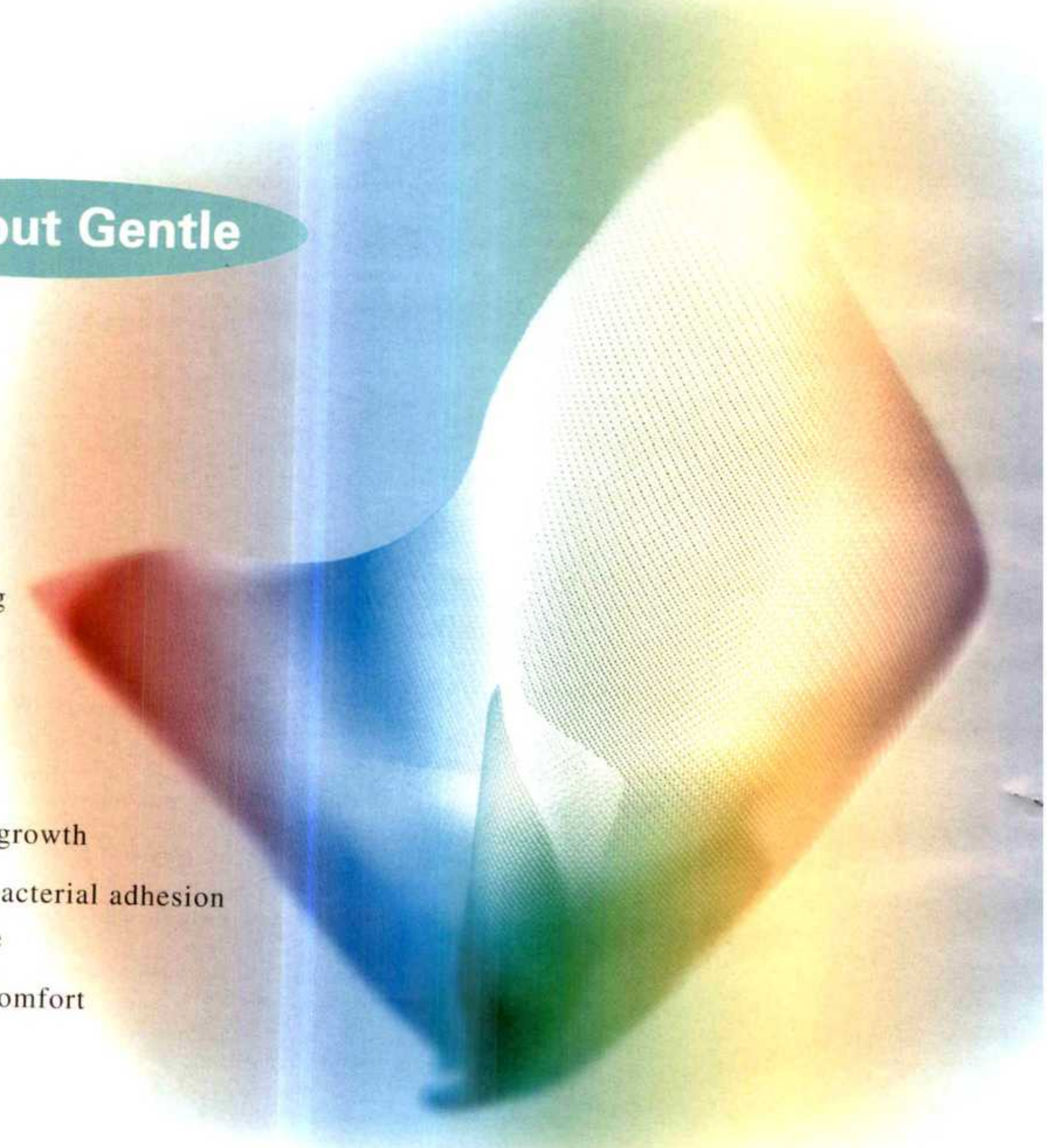

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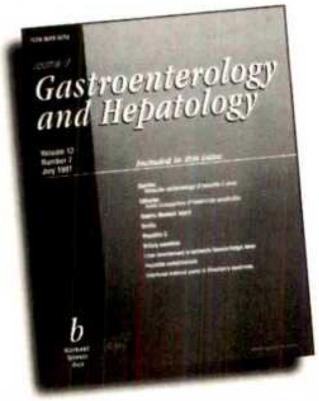

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Leading articles

Audit of the surgeon: problems and perspectives

The Society of Cardiothoracic Surgeons of Great Britain and Ireland has recently decided to monitor the performance of its members. Although the need for such audit is clear[1], a note of caution is needed about methodology. Concern arises from my own experience of auditing a personal series of 243 consecutive elective operations for abdominal aortic aneurysm, carried out between 1984 and 1998 in a district general hospital in North West Wales. There were 203 men and 40 women; 15 per cent of the patients were over 80 years old and several had severe co-morbidity. The overall 30-day mortality rate was 5·3 per cent; the mortality rate for patients aged under 80 years was 3·8 per cent, whereas for those over 80 years old it was 14 per cent. These are similar figures to death rates reported in the literature[2–5]. As this is one of the largest personal series of elective aneurysm operations in the literature and with acceptable mortality figures, I might be considered an expert in the management of aneurysm. Yet the last three patients in the audit died! In fact they represented the first three patients of 1998 and all succumbed to non-surgical pathology: one major stroke, one adult respiratory distress syndrome and one methicillin-resistant *Staphylococcus aureus* pneumonia.

So if I had been appointed as a consultant surgeon in January 1997 my operative mortality rate would have been 16 per cent, and if appointed in January 1998 it would have been 100 per cent. This surely would have been enough to raise the eyebrows of some hospital managers with thoughts of incompetence. It might even have led to suspension from clinical duties, at least until such time as a full investigation had been completed.

There is a major risk that fear of such consequences might discourage a surgeon from operating on high-risk cases. Consider one of my patients, a 94-year-old who had been followed up for 3 years with an expanding abdominal aortic aneurysm. When it reached a diameter of 7 cm he stated that he would rather die on the operating table than wait for death at home. His son agreed. The operation was technically straightforward, but on clamp release he suffered a massive myocardial infarction and died. Yet many 80 year olds can lead a very active and extended life after vascular surgery, and one of good quality[6–8]. With too vigorous an audit or an audit by the wrong people there is a grave danger that all high-risk patients and the elderly will be denied surgery.

Another factor of importance is the role of the team as a whole. Perhaps it should not simply be the surgeon who is audited, but surgeon, anaesthetist, intensive therapy unit staff and others. I have been privileged to have just one excellent anaesthetist for most operations and this is the ideal situation which should be adhered to where possible, but not all surgeons are so lucky. It is worth remembering that few elective aneurysm deaths result from technical operative causes[4].

The critical questions are who should conduct the audit and how should a problem be handled? The Society of Cardiothoracic Surgeons plans to collect anonymous data which will be ranked to show the surgeon how he or she is personally performing with respect to the mean. Although this is helpful, it is not a complete answer. What action does the surgeon take if it is evident that he or she is performing below the accepted standard? To whom goes the call for help? The General Medical Council (GMC) in the UK has instituted commendable measures to assist[9], but is a surgeon worried about personal performance likely to call the GMC? The GMC Guidelines refer to a non-surgeon 'screener'. Is a cardiac surgeon or a vascular surgeon likely to feel that he or she will receive a fair hearing from a non-surgeon? What alternatives are there?

There is an old fashioned idea in Britain's National Health Service of the 'three wise men'. This system was designed to help doctors who became ill and involves consultation with the three senior colleagues in the same or related fields as the affected practitioner. I suggest that a similar system might be applied nationally for the surgeon accused of poor performance. Specialist societies, for instance the

Vascular Surgical Society of Great Britain and Ireland, might appoint up to five senior and respected consultants from a mixture of district general and teaching hospitals to act in such a capacity. This group could publicize their existence to all medical directors, chief executives and consultants, as well as to the GMC. Any queries from hospital management or individual consultants would be dealt with by up to three of the group for the appropriate specialty. Their role would be quiet investigation, support and even suggestions for extra training. What could be better than saying 'I'll go through the patient selection and operation with you'? More importantly, these experienced clinicians would be able to help managers see pitfalls in the uncritical acceptance of what may be, on first appearance, the hardest statistic of all – dead or alive.

Introducing such a system is of paramount importance. It would have implications for recruitment to all 'high stress to the surgeon and high risk to the patient' types of procedure. With trends towards reducing the period of postgraduate training in many countries, there are likely soon to be many more troubled young surgeons. Audit needs to become an ally of good practice, not a threat to the most vulnerable patients and their doctors.

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Cryoablation of liver tumours

Primary and secondary tumours of the liver are responsible for a large number of cancer-related deaths worldwide. Unfortunately, only a fraction of these are amenable to resection, the only treatment that may result in a cure. For example, of 131 000 new patients with colorectal cancer in the USA each year, nearly half go on to develop hepatic metastases during the course of their illness; 80 per cent of these lesions will not be resectable. The usual approach of the physician towards patients with irresectable lesions is either resignation or an aggressive attempt at therapies of doubtful benefit. Among the options available for treatment of irresectable tumours confined to the liver, cryoablation has gained widespread popularity before being validated in a clinical trial.

Cryoablation of cancerous tissues has evolved substantially since the first description by James Arnott[1]. Recent advances in cryogenics and delivery of refrigerants have facilitated the treatment of lesions located in the brain, eye and prostate. With the development of intraoperative ultrasonography, cryoablation of hepatic lesions has become an appealing technique. When used together, cryoprobes can be guided accurately into tumours, the freeze-front closely monitored for the extent of tissue frozen; with thermocouples, the temperature at the edge of the tumours can be monitored accurately. An advantage of cryoablation over other methods of interstitial therapy is the ability to destroy multiple as well as large lesions up to 10 cm. However, the benefits of treating such lesions remain unclear.

Despite technical improvements, several important concerns remain. First, cryoablation of lesions close to the vena cava and other large vessels is difficult as circulating blood behaves like a heat sink and prevents adequate freezing. Second, laparotomy is essential for cryoablation as most lesions are inaccessible laparoscopically. Techniques for cryoablation through laparoscopic or percutaneous routes are not adequately developed and may result in freezing of adjacent tissues leading to devastating complications. Third, despite the simultaneous use of two or more probes, the procedure is time consuming and therefore expensive when treating multiple lesions as each lesion requires two freeze-thaw cycles of approximately 40 min to induce cell death[2]. Finally, up to 10 per cent of patients may experience major complications[3] including bleeding, localized abscess, bile collections and fistula, all of which may require further interventions[3,4]. Attempts to cryoablate large volumes of liver have led to severe complications such as acute renal failure from myoglobinuria, disseminated intravascular coagulation or air embolism[5] and death from hepatic failure.

While data on the long-term outcome of patients treated with cryoablation are limited, some have reported impressive results. For example, Zhou *et al.*[6] reported a 5-year survival of 49 per cent following cryoablation in patients with irresectable hepatocellular carcinoma less than 5 cm in size. Others have noted a 2-year disease-free survival rate of 65 per cent[7]. Of note, concurrent cirrhosis is not a contraindication to cryoablation if patients are well compensated (Child A or B and without coagulopathy). Experience with cryoablation for hepatic metastases from colorectal tumours has been different and controversial. Ravikumar *et al.*[8] reported a 2-year survival of 78 per cent and a disease-free survival rate of 39 per cent. Similarly, Morris and others[9] have noted 3-year survival rates comparable to those after resection when the carcinoembryonic antigen levels were reduced to normal after cryoablation. In contrast to these reports, Bismuth and colleagues have noted a 44 per cent local recurrence despite adequate cryoablation[7]. The problems with most studies for irresectable hepatocellular carcinoma and for metastatic disease include the lack of appropriate controls, small sample size, limited follow-up and variability in size, number and aetiology of hepatic lesions. Thus, meaningful comparisons between studies are difficult.

While controversy remains about the curative potential of cryoablation, from current experience it is clear that it should not be used for palliative purposes except for metastases from neuroendocrine tumours. Cryoablation of functional neuroendocrine hepatic metastases, alone or in combination with resection, has resulted in dramatic improvements when 70–90 per cent of the hepatic lesion is destroyed[10]. This approach is particularly useful for patients with lesions resistant to chemotherapy.

Based on the current experience, the following guidelines are suggested:

1. Cryoablation should be considered only for irresectable lesions as resection remains the preferred choice of treatment for liver tumours. Palliative use should be restricted to functional neuroendocrine tumours.
2. Two freeze-thaw cycles are essential for inducing cell death. The freeze cycle should be continued for at least 15 min after the desired tissue is frozen.
3. For hepatocellular carcinoma and metastatic colorectal tumours, cryoablation should be used only with an intent to cure (i.e ensuring that a 1-cm rim of normal hepatic tissue beyond the tumour is included), as no survival advantage is noted with incomplete ablations.
4. Cryoablation may be used for ablating positive margins when further resection cannot be done.

Multimodality approaches are being evaluated to deal with failures and complications of cryoablation. Combining the technique with continuous hepatic-arterial infusion of chemotherapeutic agents may decrease intrahepatic recurrence at the same or new sites in patients with metastatic colorectal tumours[9]. Similarly, preoperative chemoembolization of hepatocellular carcinoma may decrease local recurrence and bleeding following cryoablation. Emerging strategies, such as gene therapy and immunotherapy, may find applications as adjuvant therapies to cryoablation in the future.

The relative ease of the technique compared with resection makes it prone to inappropriate use, in particular for lesions that can be resected or where no obvious benefit can be achieved. A cautious approach is necessary until results from well controlled clinical trials are available to determine the benefits of cryoablation.

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Review

Antireflux surgery in the laparoscopic era

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Background The recent development of laparoscopic techniques for fundoplication has created renewed interest in surgery for gastro-oesophageal reflux disease, leading to reports of large clinical series from many centres. However, controversy remains about technical aspects of laparoscopic antireflux surgery, with no consensus yet reached about a standard operative technique. It is important, therefore, to reassess critically the results of laparoscopic surgery for reflux disease, so that its current status can be determined.

Methods Published outcome studies for laparoscopic antireflux surgery, as well as selected studies from the era of open antireflux surgery, were reviewed to assess outcomes.

Results The results of case series for laparoscopic antireflux surgery with short- and medium-term follow-up, as well as the early results of randomized trials, confirm that this approach reduces the early overall morbidity of surgery for reflux disease. However, certain complications may be more common, for instance paraoesophageal hiatus herniation, pneumothorax and oesophageal perforation, requiring surgeons to use specific strategies which can help to avoid these problems. Published studies and trials do not support the routine or selective application of a posterior partial fundoplication technique or routine division of the short gastric vessels during Nissen fundoplication.

Conclusion At present, a short loose Nissen fundoplication performed laparoscopically, with or without division of the short gastric vessels, is an appropriate surgical approach for gastro-oesophageal reflux disease. However, long-term outcomes following laparoscopic antireflux surgery will not be available for some years, and must be awaited before the final status of the various laparoscopic techniques can be confirmed.

All practising surgeons are aware of the recent and rapid development of minimal access surgical techniques, largely made possible by the development of new equipment and technology for the operating theatre. In a short time period laparoscopic cholecystectomy has become the standard treatment for symptomatic gallstone disease in the developed world[1–3]. Procedures such as laparoscopic inguinal hernia repair and laparoscopic colonic resection, however, have failed to achieve a similar level of acceptance[4,5]. These procedures have been criticized because of their potential to cause new and different complications from those seen after open approaches[6,7].

The current status of laparoscopic antireflux surgery may lie somewhere between these positions, although it is rapidly gaining acceptance as the preferred surgical treatment for severe gastro-oesophageal reflux disease. Since laparoscopic Nissen fundoplication was first described in 1991 by both Geagea[8] and Dallemagne *et al.*[9] laparoscopic antireflux surgery has been embraced enthusiastically in many centres[10–16]. Nevertheless, it remains under close scrutiny, until satisfactory long-term outcomes have been established. While long-term outcomes will not be available for many more years, the early results of laparoscopic antireflux procedures have now been reported by many groups[17–40]. It is appropriate, therefore, to review the current status of laparoscopic antireflux surgery to determine how the surgical management of gastro-oesophageal reflux disease should best be approached.

Status of open Nissen fundoplication

Fundoplication was first described by Nissen in 1956[41] following the serendipitous discovery that a fundal patch, used to reinforce an oesophageal suture line, also corrected gastro-oesophageal reflux. While achieving good control of pathological reflux in the majority of patients[42], an incidence of adverse sequelae has led to the subsequent modification of Nissen's original technique. Shortening the fundoplication length to 1–2 cm, dividing the short gastric vessels to achieve full mobilization of the gastric fundus, calibration of a loose fundoplication over a large intraoesophageal bougie and modification of the complete fundoplication to one of a number of partial fundoplication variants have all been advocated[43–48]. Few of these modifications, however, have been evaluated within the context of prospective randomized trials[49–54].

Following four decades of experience with open antireflux procedures, long-term outcomes following open surgery have been well described (*Table 1*). Postoperative hospital stay ranges from 7 to 14 days[45,50], short-term morbidity is acceptable[43,54], and long-term success is achieved in the majority of patients[43,55]. Rossetti and Hell[42] reported that 87·5 per cent of patients, followed for more than 10 years after a 360° fundoplication without short gastric vessel division, were free from reflux symptoms and adverse sequelae. Similarly, DeMeester *et al.*[43] reported a 91 per cent success rate for the Nissen

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Table 1 Expected outcome following open Nissen fundoplication

Short term	
Complication rate (%)	10–20[55]
Incidental splenectomy (%)	1–3[43,54,55]
Mortality rate (%)	< 0–1[43,56]
Length of hospital stay (days)	7–14[50]
Long term	
Control of reflux at ≥ 5 years (%)	> 90[43,51,56]
Good or excellent long-term outcome (%)	90[42,43,51,57]
Long-term troublesome dysphagia (%)	< 5[43,56]

fundoplication procedure at mean follow-up of 45 months. Other studies describe long-term success rates of 85–90 per cent following open antireflux surgery[45,51,57,58]. Recently, Luostarinen *et al.*[55] reported that 71 per cent of a series of 25 patients who underwent the combination of Nissen fundoplication and pyloroplasty remained free from reflux 20 years or longer after the original procedure.

Adverse outcomes

Adverse outcomes following open Nissen fundoplication include persistent dysphagia and gas bloat syndrome[43,54,58]. Many patients also have troublesome early dysphagia[51] which resolves as follow-up matures. The interpretation of dysphagia symptoms, however, can be difficult, because different methods of clinical assessment and scoring are used in the various available studies. There is also the potential for introduction of significant bias by clinician investigators, particularly if follow-up is performed by the operating surgeon. Despite these difficulties, it is likely that the incidence of persistent long-term troublesome dysphagia is less than 5 per cent following Nissen fundoplication[43,51,54,57,58]. Uncontrolled reports suggest that the performance of a partial fundoplication variant may reduce this incidence[45]. However, this proposal has not been supported by the results of published randomized trials[50–53,58] (see below).

Randomized trials in the era of open fundoplication

Despite the large number of publications describing fundoplication outcomes in the era of open surgery, few randomized trials have been conducted (*Table 2*). Three trials have compared Nissen fundoplication with posterior partial fundoplication[51–53,64], and one has compared Nissen fundoplication with Hill and Belsey procedures[51]. None of these found any significant increase in the likelihood or severity of dysphagia following Nissen fundoplication, compared with a posterior partial fundoplication procedure. However, with the exception of the study from Lundell *et al.*[51,52], which enrolled 137 patients, all of the studies assessing the partial fundoplication variants enrolled small patient numbers, which were inadequate to allow statistically valid conclusions to be drawn. Perhaps surprisingly, the incidence of dysphagia in two of these studies[51,53] was actually greater following posterior partial fundoplication, although differences failed to reach statistical significance.

Table 2 Randomized trials investigating open antireflux surgery

Trial	No. of patients entered
Nissen *versus* posterior partial fundoplication[51–53,64]	137, 33, 52
Nissen *versus* Hill *versus* Toupet[50]	45
Nissen *versus* Angelchik prosthesis[54,59,60]	61, 50, 48
Nissen *versus* ligamentum teres cardiopexy[61]	20
Nissen *versus* ranitidine[62]	247
Nissen with *versus* without division of short gastric vessels[46,63]	25

Only the trial of Lundell *et al.*[51,52] reported any significant differences. While dysphagia was less frequently found at 3 months after partial fundoplication, differences were not noted at other follow-up intervals. Flatulence was more frequent at 2 and 3 years after Nissen fundoplication but not at other earlier or later time intervals. Reflux control was identical. Reoperation was more frequent after Nissen fundoplication, because five of the Nissen group underwent reoperation for a postoperative paraoesophageal hernia, although this did not reach statistical significance. Significantly, hiatal repair was only performed infrequently in this trial and in only one of the patients who required revision. It is possible that the reoperation rate could have been reduced in the Nissen group if the hiatus had been repaired routinely at the original procedure, a step which is now advocated for all laparoscopic Nissen fundoplications[65]. An overall assessment of all of these randomized trials has failed to demonstrate important advantages to support the routine application of a posterior partial fundoplication[66], although this conclusion might be disputed by supporters of posterior partial fundoplication techniques. However, this cannot be extrapolated to the alternative technique of anterior partial fundoplication; it is possible, but certainly not proven, that this modification could result in outcome improvements[45,67].

Other small randomized studies have compared Nissen fundoplication with insertion of the Angelchik prosthesis[54,59,60], and Nissen fundoplication with the ligamentum teres repair[61], demonstrating advantages for Nissen fundoplication[54,59,61]. While these studies also enrolled only a small number of patients, because of the magnitude of the differences identified they did reveal distinct advantages for the Nissen procedure. Hill *et al.*[54] demonstrated in a study involving 61 patients that the Angelchik prosthesis was associated with a higher likelihood of surgical revision. A similar outcome was described by Kmiot *et al.*[59] in a study involving 50 patients. Janssen *et al.*[61] randomized 20 patients to undergo either Nissen fundoplication or ligamentum teres cardiopexy. By 12 months' follow-up, six of the ten patients who underwent the ligamentum teres repair required further surgery for recurrent reflux, compared with one in the Nissen group. The results of the ligamentum teres repair were so poor that continued use of this procedure by either laparoscopic[68] or open techniques cannot be justified.

Luostarinen *et al.*[49,63] recently reported the results of a small trial of division *versus* no division of the short gastric vessels during open Nissen fundoplication. Twenty-five patients were entered and no significant outcome differences were demonstrated. This study could be criticized for failing to enrol enough patients to demonstrate potential outcome differences reasonably.

Spechler[62] reported the only trial to compare operative with non-operative therapy for reflux. In this study, 247 patients were randomized to undergo continuous medical therapy with a histamine receptor blocker, medical therapy only for symptoms, or open Nissen fundoplication. Forty patients withdrew following randomization, 24 from the surgery group; 176 were followed for at least 1 year and 106 for 2 years. Overall patient satisfaction was highest in the surgical group at both the 1- and 2-year follow-up intervals. However, neither the surgical approach nor the medical treatment in this study would now be regarded as optimal management for reflux disease.

Indications for antireflux surgery

The laparoscopic approach to antireflux surgery now offers a potentially more acceptable surgical option for patients with gastro-oesophageal reflux because of the reduced postoperative pain and more rapid recovery. This has led many symptomatic patients, who previously did not wish to undergo open antireflux surgery, now to request a laparoscopic fundoplication[27,69]. In the light of this many centres are rapidly gaining experience with laparoscopic antireflux surgery[19,20,24,26,27,29,37,40,70].

An expanded role for surgical management has also been proposed, with some surgeons now claiming that earlier surgical correction of pathological reflux may prevent progression to the complications of Barrett's oesophagus and stricture formation[69–71]. It should be recognized, however, that this opinion is controversial and is not yet supported by reported outcomes. That successful results cannot be guaranteed following any variant of antireflux surgery mandates an ongoing policy of careful patient selection. Abnormal gastro-oesophageal reflux disease should be demonstrated before surgery either by ambulatory 24-h pH monitoring or by the presence of erosive oesophagitis at endoscopic examination[72,73]. Patients should also have either ongoing reflux symptoms despite adequate medical management or they should have expressed a desire to avoid lifelong medication. Despite the advocacy for the above expanded role, many surgeons believe that indications for surgical management remain unchanged in the laparoscopic era[19–21,40].

Appropriate situations for the application of a laparoscopic approach

In many surgeons' early experience, difficulties were encountered with laparoscopic antireflux surgery in patients who had a large left lobe of liver, in patients with a large paraoesophageal hiatus hernia, in the morbidly obese, and in patients who had undergone previous upper abdominal surgical procedures[21,22,24,27]. However, recent reports suggest that many of these problems can be overcome[20,26,28]. Many surgeons have now confirmed the feasibility of repair of giant paraoesophageal hernias[74–82], and improved liver retraction devices, such as the Nathanson Liver Retractor (Cook Australia, Brisbane, Australia) now facilitate excellent and stable exposure of the oesophageal hiatus, even in the presence of an enlarged liver[20]. Adhesions secondary to previous upper abdominal surgery no longer often present significant difficulties[19,25,30,83], except in patients who have undergone previous proximal gastric or hiatal surgery[25,65,84,85].

Early results and complications following laparoscopic fundoplication

The first large study to report outcomes following laparoscopic fundoplication was published by Cuschieri *et al.*[16] in 1993, who described promising results in a multicentre series of 116 patients. Further large single-centre experiences of more than 100 patients have been published since[17,19–21,23–25,27–30,38,40,70,86], with follow-up of 2–3 years in some later studies[26–28,70]. The clinical outcomes from the larger published series are summarized in *Table 3*. Mean or median operating times vary from 30 to 185 min and complication rates range from 2 to 26 per cent[19,20,26,33]. Surgical revision has been needed in a small group of patients in most series. Variation in revision rates may be influenced by the effect of the institutional learning curve, technical factors associated with the choice of surgical technique, and

Table 3 Outcome after laparoscopic fundoplication

Reference	Year	Procedure performed	No. of patients	Conversion rate (%)	Operating time (min)	Complication rate (%)	Recurrent/on reflux (%)
Cuschieri *et al.*[74]	1992	LNF –	116	0·9	150*	13	8·6
Jamieson *et al.*[21]	1994	LNF –	155	12·3	120†	9·7‡	1·9
Watson *et al.*[26]	1996	LNF –	174	9·2	80†	2·3	0·7
Weerts *et al.*[40]	1993	LNF +	132	3·3	118*	7·5	1·1
Dallemagne *et al.*[38]	1995	LNF +	368	1·4	107*	4·0	3·2
Hinder *et al.*[19]	1994	LNF +	198	3·0	150†	11·6*‡	8·0
Cadiere *et al.*[22]	1994	LNF +	80	4	150†	9	0
Hallerback *et al.*[33]	1994	LNF –	60	15	110†	10	2
Fontaumard *et al.*[29]	1995	LNF –	148	0	90†	12·5	0
McKernan and Champion[30]	1995	PPF	283	0·5	82*	3·5	0·5
Gotley *et al.*[20]	1996	LNF ±	200	4·5	149†	8·0	0·5
Anvari *et al.*[24,86]	1995, 1996	LNF –	195	2·0	68*	8·9	0·6
Hunter *et al.*[27,28]	1996	LNF ±	300	1·5	185*	11·7	0·7
Cattey *et al.*[87]	1996	LNF +	100	2·0	101*	8·0	6·5
Coster *et al.*[34,70]	1995, 1997	LNF – /PPF	231	2·2	30*	12·0	6·0
Medina *et al.*[88]	1996	LNF +	74	1	139*	4‡	7
Bittner *et al.*[14]	1994	LNF –	35	14	110*	26	4
Pitcher *et al.*[15]	1994	LNF ±	70	3	186*	4	0
O'Reilly *et al.*[89]	1996	PPF	100	0	—	4·0	0
Mosnier[90]	1995	PPF	51	2	140†	10	4

*Mean; †median; ‡postoperative death. LNF –, laparoscopic Nissen fundoplication without division of short gastric vessels; LNF +, laparoscopic Nissen fundoplication with division of short gastric vessels; LNF ±, laparoscopic Nissen fundoplication with selective division of short gastric vessels; PPF, laparoscopic posterior partial fundoplication

Table 4 Complications after laparoscopic antireflux surgery

Pneumothorax[91–95]
Pneumomediastinum[96,97]
Pulmonary embolism[21,98,99]
Injury to major vessels[100]
Paraoesophageal hiatus hernia[65,98,101]
Hiatal stenosis[102]
Mesenteric thrombosis[88,103]
Oesophageal perforation[23,98,104–106]
Gastric perforation[21,98,104]
Duodenal perforation[19]
Bowel perforation[106]
Cardiac laceration[107]
Pleuropericarditis[108]

different criteria used for the recognition and classification of complications in different reports. For example, dysphagia rates may depend on the choice of clinical measure used to determine postoperative dysphagia and who applies the chosen measure; the operating surgeon may elicit a different response from an independent investigator.

Laparoscopic Nissen fundoplication is reported to control reflux symptoms in 91–100 per cent of patients followed for up to 2 years[26,28], results which mirror previous experience with open antireflux surgery[42,43,57,58]. Postoperative hospital stays have been short in all published reports, with mean/median stays ranging from 2 to 5 days[19,20,26,27,30]. Overall results from these case series suggest that laparoscopic antireflux surgery is effective and that it results in an overall reduction in short-term morbidity associated with surgery for reflux. However, several complications unique to the laparoscopic approach have been described (*Table 4*). Some of these have now become significant in the current medicolegal environment; in particular, complications which have a risk of more than 1 per cent should be explained to patients before surgery. The specific risks of postoperative paraoesophageal hiatus hernia, dysphagia requiring further surgery and gastrointestinal perforation should be balanced against the advantages of the laparoscopic approach.

Pneumothorax

Left-sided pneumothorax may occur at operation following injury to the left pleural membrane caused by high retro-oesophageal dissection[91–95]. The risk of this may be up to 2 per cent, although it is likely that careful dissection technique and experience reduces its likelihood. Its occurrence does not require the placement of a chest drain, as the carbon dioxide gas in the pleural cavity is rapidly reabsorbed at the completion of the procedure. Pneumomediastinum is also described[96,97], although it is rarely a clinical problem.

Vascular injury

Vascular injuries to the inferior vena cava, the left hepatic vein, the abdominal aorta and the inferior phrenic vessels have all been reported[100,109]. It is possible that this complication is associated with a combination of aberrant anatomy, inexperience and the excessive use of monopolar diathermy cautery dissection. Intraoperative bleeding more commonly follows inadvertent laceration of the left lobe of the liver by a laparoscopic liver retractor or other instrument. Haemorrhage may also occur from poorly secured short gastric vessels during fundal mobilization. A rare complication is cardiac tamponade due to laceration of the right ventricle by a liver retractor[107].

However, the overall risk of perioperative haemorrhage associated with antireflux surgery is probably reduced by the laparoscopic approach[19,21]. The risk of splenectomy due to inadvertent splenic injury during Nissen fundoplication is dramatically reduced by the laparoscopic method[19,25]. While splenectomy rates of 1–3 per cent[43,54,55] have been noted in association with open fundoplication, splenectomy is a rare event following laparoscopic fundal mobilization. It is likely that the more precise dissection and better anatomical exposure afforded by the minimally invasive approach minimizes the likelihood of inadvertent splenic trauma.

Paraoesophageal hiatus herniation

Paraoesophageal hiatus herniation has been regarded as an occasional finding, usually presenting in the late follow-up period after open fundoplication[51]; however, it has also been suggested that its incidence may be greater than previously recognized[51]. On the other hand, most large series of the laparoscopic procedure report an incidence of paraoesophageal herniation of up to 7 per cent, particularly in the immediate postoperative period[18–21,65,101]. That this complication is more likely to occur after laparoscopic surgery may be due to a tendency to extend laparoscopic oesophageal dissection further into the thorax[23], an increased risk of breaching the left pleural membrane[91–95] and the effect of reduced postoperative pain. Reduced pain may permit more abdominal force to be transmitted to the hiatal area during coughing, vomiting or other forms of early exertion, thereby pushing the stomach into the thorax[65]. It seems likely that routine hiatal repair[20,65] and liberal use of antiemetics will reduce the risk of this problem. It is also possible that some of the apparent variation in incidence reflects differences in the steps taken by different investigators to seek the diagnosis.

Dysphagia

Early severe dysphagia requiring surgical revision has been described in a number of series[18,20,84,85,98,102]. Conversion of a Nissen fundoplication to a posterior partial fundoplication has been performed for troublesome dysphagia by both open and laparoscopic techniques, usually with success[20,83,84,98]. Excessive tightening of the oesophageal hiatus, another potential cause of early dysphagia, may be difficult to assess at operation because of reduced tactile feedback during laparoscopic surgery. This can be corrected by early laparoscopic reintervention to release one or more hiatal sutures. Late narrowing of the oesophageal hiatus due to postoperative scarring, even in patients not undergoing hiatal repair, has also been described[102]. It is possible that this complication results from an idiosyncratic response to diathermy dissection. Correction requires widening of the diaphragmatic hiatus by either open or laparoscopic means.

Pulmonary embolism

Pulmonary embolism may occur after laparoscopic antireflux surgery[21,98,99]. This is likely to result from a combination of primarily mechanical factors. The combination of head-up tilt of the operating table, intra-abdominal insufflation of gas under pressure and elevation of the legs of patients in stirrups may greatly reduce blood flow in leg veins[110]. Coagulation changes associated with surgery are not altered by the application of laparoscopic techniques[99]. To prevent pulmonary embolism antithromboembolism prophylaxis is mandatory.

Perforation of the gastrointestinal tract

Perforation of the oesophagus, stomach, duodenum and bowel have all been described during laparoscopic antireflux surgery[19,21,23,98,104–106]. While perforation of the small bowel and the colon may be related to laparoscopic access in general, oesophageal and gastric perforations are specific risks of minimally invasive antireflux surgery, with an incidence of approximately 1 per cent in most series[19,21,23,98,104–106]. Perforation of the posterior wall of the oesophagus may occur when dissecting the posterior aspect of the oesophagus with laparoscopic instruments[104,111]. The anterior oesophageal wall is at risk when a bougie is passed to calibrate the tightness of a Nissen wrap[104,105]. Gastric perforation is usually an avulsion injury of the gastric cardia due to rough handling by the surgical assistant or the use of inappropriate grasping instruments to retract the stomach[21,104]. These injuries can be repaired by sutures, applied either laparoscopically or by an open technique. Awareness of the potential for these injuries to occur should allow the surgeon to institute measures to reduce their likelihood[111].

Death

Only three deaths following laparoscopic antireflux procedures[19,88,103] have been reported, confirming the safety of this approach. Hinder *et al.*[19] described a patient who died from peritonitis and sepsis from a duodenal perforation, presumably caused by an instrumental injury occurring outside of the restricted field of view provided by the laparoscope. Mitchell and Jamieson[103] described an instance of thrombosis of both the superior mesenteric artery and the coeliac axis. This rare complication has also been noted after laparoscopic cholecystectomy[112], suggesting the possibility that it may be related to the use of positive pressure insufflation[113]. A further case of infarction of the liver following laparoscopic fundoplication was reported by Medina *et al.*[88].

The learning curve

As with other laparoscopic procedures, there is little doubt that laparoscopic antireflux surgery requires surgeons to learn a new range of operating skills. The need for laparoscopic suturing and specific dissection techniques introduces an additional layer of complexity over that of laparoscopic cholecystectomy. There is a definable learning curve, during which procedures are associated with extended operating times and an increased risk of complications[114]. An institutional learning curve of 50 procedures and individual learning curves of 20 operations were identified from an initial experience of 280 laparoscopic antireflux procedures reported by Watson *et al.*[114]. Importantly, however, this study demonstrated that the adverse effects of the learning curve could be prevented if new surgeons commenced laparoscopic antireflux surgery under the direct supervision of an experienced surgeon. Furthermore, outcomes following laparoscopic Nissen fundoplication have been shown to be significantly better in the hands of experienced surgeons[26].

Laparoscopic *versus* open surgery

Although laparoscopic approaches reduce short-term surgical morbidity, is it reasonable to expect better long-term outcomes than those following equivalent open procedures? Technical modifications introduced to facilitate various laparoscopic approaches might result in better or, conceivably, worse long-term outcomes. Until the results of long-term studies are available, the true outcome of laparoscopic antireflux surgery and its status compared with open antireflux surgery must remain uncertain.

Non-randomized comparisons

Few direct comparisons of clinical outcome, surgical morbidity and cost effectiveness have been attempted between early series of laparoscopic Nissen fundoplication and open surgical experience (historical or otherwise) within single institutions[115–121]. Given the constraints of the non-randomized research methodology used in almost all of these studies, a fair comparison of laparoscopic and open techniques is difficult. All published studies report that laparoscopic antireflux surgery reduces hospital treatment costs and early surgical morbidity[115–121]. Similar advantages were identified by non-randomized studies which compared laparoscopic inguinal hernia repair, appendicectomy and cholecystectomy with their equivalent open procedures[3,122,123]. However, these advantages have not all been supported by prospective randomized trials[124–126].

The non-randomized comparisons between open and laparoscopic fundoplication are summarized in *Table 5*. Although laparoscopic surgery generally requires more operating time than equivalent open surgical procedures, one group[119] reported that the laparoscopic approach was actually quicker. The incidence of postoperative complications was reduced, the length of postoperative hospital stay was shortened by 3–7 days, and patients returned to full physical function between 6 and 27 days earlier following laparoscopic antireflux surgery. Overall efficacy of reflux control was similar.

Four non-randomized studies have compared the cost of laparoscopic antireflux surgery with an open procedure, all within the American health care setting[116,120,121,127]. No cost comparisons have been reported from Europe or Australasia. The outcome of these comparisons is summarized in *Table 6*. All of these studies demonstrated that laparoscopic Nissen fundoplication is cost effective within the American health financing system. A cost saving of between US$555 and US$8906 per case was achieved by the laparoscopic approach, owing to reduced postoperative hospital stay costs. Operating theatre costs were increased by laparoscopic surgery. The study reported by Laycock *et al.*[121], however, can be criticized as it compared a laparoscopic Nissen fundoplication with a Belsey repair through an open thoracotomy incision. It is difficult to translate the potential savings identified in these studies into savings in other health care systems. The analyses may also underestimate the potential benefits of laparoscopic fundoplication as they do not take into account potential community savings which might be

Table 5 Comparison of laparoscopic and open fundoplication: non-randomized studies

Reference	Year	No. of procedures	Operating time (min)	Hospital stay (days)	Complications (%)	Time off work (days)	Good outcome (%)
Champault *et al.*[119]	1996						
Laparoscopic		32	125	5·4	–	21	91
Open		29	140	8·9	–	38	91
Frantzides and Carlson[115]	1995						
Laparoscopic		36	186	1·8	3	–	97
Open		29	168	9·2	17	–	100
Richards *et al.*[116]	1996						
Laparoscopic		72	113	1·5	11	16	–
Open		160	100	6·1	37·5	43	–
Rattner and Brooks[117]	1995						
Laparoscopic		74	173	4·0	–	24	–
Open		12	169	8·1	–	30	–
Peters *et al.*[118,120]	1995						
Laparoscopic		34	221	5·8	–	–	94
Open		47	165	8·8	–	–	95

Table 6 Comparison of the cost of laparoscopic and open fundoplication

Reference	Year	No. of patients	Operating room cost (US$)	Bed cost (US$)	Total hospital cost (US$)
Richards *et al.*[116]	1996				
Laparoscopic		72	2 324	2 007	4 331
Open		160	1 287	7 329	8 616
Incarbone *et al.*[120]	1995				
Laparoscopic		11	16 730	9 904	26 634
Open		9	14 283	12 906	27 189
Iglesias *et al.*[127]	1997				
Laparoscopic		25	3 253	7 848	11 101
Open		34	2 724	11 562	14 286
Laycock *et al.*[121]	1995				
Laparoscopic		20	6 077	9 316	15 393
Open		20	5 292	19 007	24 299

achieved by any shortened convalescent period. Any reduction in the time patients spend away from productive work as a result of the laparoscopic approach could lead to important community savings. However, it remains to be seen whether major cost savings can be demonstrated by prospective randomized trials.

Randomized comparisons

Three prospective randomized controlled trials which compared a laparoscopic Nissen fundoplication with its open surgical equivalent have been reported[128–130], two as published abstracts only. All confirm that the overall morbidity of surgery for reflux, the incidence of complications, and the postoperative hospital stay are reduced by the laparoscopic approach. Laine *et al.*[128] recently published a study which enrolled 110 patients. Hospital stay was halved from 6·4 to 3·2 days, patients returned to work earlier (37 *versus* 15 days) and operating time was prolonged by 31 min (from 57 to 88 min). Control of reflux symptoms was similarly effective, although outcomes beyond 12 months after surgery were not described. Two further smaller studies[129,130], published as abstracts only, reported similar outcomes. Interestingly, only a 1-day reduction in hospital stay was noted in both of these trials, because patients in the open surgical groups were discharged predominantly on the fourth day after operation. This underlines the fallacy of comparing data across time periods, as it is clear that even patients undergoing open operations are being discharged earlier than was the case in the past. The most significant advantage for the laparoscopic approach, however, was the time taken for patients to return to normal physical activity, which was decreased from 8 to 2 weeks[129], confirming significant community advantages for the laparoscopic method. The early results of all of these trials confirm advantages for the minimally invasive approach, albeit less dramatic than the advantages claimed in non-randomized studies.

Reoperative surgery following laparoscopic fundoplication

Most large series of laparoscopic antireflux surgery describe an incidence of adverse outcomes requiring subsequent surgical revision[18–20,28,84]. The incidence varies with the length of postoperative follow-up and the criteria used for reporting. An incidence of 2–6 per cent at short-term follow-up is usual, with many of the reoperations required to correct unique complications of the laparoscopic approach[23,65,98,101,102,104–106]. Early identification of these problems may facilitate early laparoscopic repair[22]. However, later identification, beyond the first postoperative week, often requires a more difficult open surgical procedure. This is principally because of adhesion formation and fibrosis rendering the laparoscopic option in many instances impossible[22,85,102], although undoubtedly as experience increases more patients will have revision performed laparoscopically.

Laparoscopic revision procedures performed more than 3 months after the original fundoplication have also been described[25,83]. However, the expertise and experience needed to perform these technically demanding operations is not widely available. On the other hand, laparoscopic revision within a few days of the original procedure, for complications such as postoperative paraoesophageal herniation or early severe dysphagia, are technically less demanding and may not add greatly to the overall morbidity of the laparoscopic approach[19,114]. Many surgeons recommend routine early postoperative barium swallow radiographs to enable early identification and laparoscopic correction.

Other randomized trials for laparoscopic surgery

Apart from the three randomized trials of laparoscopic *versus* open Nissen fundoplication, only four other randomized trials examining laparoscopic antireflux surgery have been published. Two of these studies compared different techniques for dividing the short gastric vessels during laparoscopic Nissen fundoplication. Laycock *et al.*[131] randomized 20 patients to have these vessels divided between metal clips or by Ultrasonic Shears (Ultracision, Smithfield, Rhode Island, USA). A time saving was demonstrated for the Ultrasonic Shears. Swanstrom and Pennings[132] also demonstrated a time saving of 10 min for the Ultrasonic Shear technique in a study involving 31 patients. Laws *et al.*[133] recently reported a trial of 39 patients randomized to undergo either laparoscopic Nissen or laparoscopic posterior fundoplication. No significant short-term differences were demonstrated between the two procedures in this small study.

Watson *et al.*[134] investigated whether division of the short gastric vessels during laparoscopic Nissen fundoplication affected postoperative outcome, in particular postoperative dysphagia. Some 102 patients were entered into a prospective double-blind randomized trial. No reduction in the incidence of postoperative dysphagia or improvement in any other outcome variable was found, suggesting that routine division of the short gastric vessels is not necessary for the satisfactory construction of a laparoscopic Nissen fundoplication. Apart from this trial and the study described by Laine *et al.*[128], there is a paucity of data from randomized trials of laparoscopic surgical procedures available to enable surgeons to determine the most appropriate technique for the performance of antireflux surgery.

Controversies and disagreements

The advent of laparoscopic antireflux surgery has focused debate between protagonists of various antireflux surgical techniques (*Table 7*). While the Nissen fundoplication remains the technique performed by the majority, a number of variants of posterior and anterior partial fundoplication, as well as other techniques, have been advocated to reduce the likelihood of postoperative dysphagia and gas bloat symptoms[68,70,135–140]. Some surgeons advocate the selective use of partial fundoplication variants for patients with oesophageal dysmotility[27,71,141,142]. Others advocate the routine application of a particular partial fundoplication variant[70,137,138].

Table 7 Unresolved issues in laparoscopic antireflux surgery

When should one apply a partial fundoplication technique?
Which partial fundoplication technique is appropriate?
Should the short gastric vessels be divided during laparoscopic Nissen fundoplication?
Should the hiatus be repaired selectively or routinely?
Should the choice of procedure be tailored to the preoperative findings?
How common is the short oesophagus and how should it be managed?

Laparoscopic partial fundoplication

The results of the trials comparing posterior partial fundoplication techniques with the Nissen technique performed by open surgical methods have been discussed previously. These studies do not suggest significant outcome differences. There is no reason to believe that these results should not apply to the relative merits of different laparoscopic methods. A randomized trial assessing an anterior partial fundoplication technique performed either laparoscopically or by an open method has not been reported, although one is under way in the authors' department.

Early case series of patients who have undergone either posterior or anterior partial fundoplication describe good or excellent early outcomes[70,89,90,135,136,138,143] with low postoperative dysphagia rates. It is necessary to be cautious when comparing different case series, however, as they may be assessed after operation by different personnel who have almost certainly used different methods of symptom assessment. Before the routine use of laparoscopic partial fundoplications can be advocated, benefits should be demonstrated by randomized trials which confirm that the incidence of postoperative dysphagia or other adverse outcomes is reduced, and that long-term efficacy is probable. Previous trials have not done this[51–53,64,133].

Division of the short gastric vessels

Following the advent of laparoscopic Nissen fundoplication, argument has intensified about whether the short gastric vessels should be divided to allow full fundal mobilization, or whether an anterior wall complete fundoplication constructed without short gastric vessel division can achieve an equally low rate of postoperative dysphagia or other adverse outcomes[86,144,145]. Because good results have been published following series of both open and laparoscopic Nissen fundoplication, performed with and without division of the short gastric vessels[19,21,42,43,86], it has been difficult to resolve from the evidence of uncontrolled case series whether division of these vessels is necessary. This problem is compounded by the lack of standardization of assessment criteria for dysphagia, which renders comparison between different published reports difficult.

The original studies which popularized division of the short gastric vessels described non-randomized comparisons of patients undergoing open surgery[43,44,56]. A study by DeMeester *et al.*[43] made two concurrent changes to the surgical technique used (division of the short gastric vessels and shortening of the wrap), making assessment of the impact of short gastric vessel division difficult. These authors claimed that shortening the fundoplication length resulted in a reduction in the incidence of persistent dysphagia and that division of the short gastric vessels resulted in improved relaxation of the lower oesophageal sphincter. A recent study of manometric *versus* clinical outcome[146] suggests that manometrically measured lower oesophageal sphincter relaxation correlates only weakly with postoperative dysphagia.

A number of surgeons have recently compared their laparoscopic experience of a Nissen fundoplication performed without dividing the short gastric vessels with their subsequent experience of dividing short gastric vessels[144,145]. In these studies laparoscopic Nissen fundoplication was performed initially without dividing the vessels. With improving laparoscopic experience, the surgeons began to divide the short gastric vessels and then compared their experience with the two techniques. Analysis of the outcomes suggested that dysphagia was more common in patients in whom the short gastric vessels were left intact[144,145]. From this it was concluded that the short gastric vessels should be divided to minimize the incidence of postoperative dysphagia. However, such analysis discounts learning curve bias[114]. An alternative hypothesis is that the dysphagia rate fell as surgeons gained experience in laparoscopic antireflux surgery. The outcomes of the prospective randomized trials reported recently by Luostarinen *et al.*[49,63] and Watson *et al.*[134] both demonstrate no significant differences. These studies provide more reliable evidence for the assessment of this issue. It is possible that the most important technical step necessary for the avoidance of postoperative dysphagia following Nissen fundoplication is to ensure a short loose wrap, irrespective of whether the short gastric vessels are divided or not.

Selective versus *routine hiatal repair*

While routine hiatal repair was not a major issue for open fundoplication, this manoeuvre has become more important for the laparoscopic approach. The high incidence of up to 10 per cent of early paraoesophageal hiatal herniation reported in patients who did not undergo laparoscopic hiatal repair[65] *versus* the lower incidence of 2–3 per cent reported in patients undergoing repair[20] suggests that this step should be routine. The overall incidence of this problem in the acute postoperative period, even in patients who underwent hiatal repair, may still be greater than that seen following open surgery. Unfortunately the minimally invasive surgeon may also have difficulty judging the degree of hiatal narrowing performed laparoscopically, with overtightening of the hiatus (which can result in severe early dysphagia) a real possibility. In the light of reported experience, it seems sensible to perform some form of hiatal repair during laparoscopic antireflux surgery.

Tailored approach to laparoscopic fundoplication

Recently, a number of surgeons have advocated tailoring the antireflux procedure according to various features assessed before operation[71,141,142,147]. Kauer *et al.*[71] and Little[141] have suggested that the laparoscopic approach should be used only for patients with simple oesophagitis and not for patients with the complications of peptic stricture formation or Barrett's oesophagus. Both authors recommend that patients with complicated disease and those with potential oesophageal shortening should undergo an open transthoracic procedure. However, these criteria for a tailored approach are not supported by the majority of surgeons performing laparoscopic antireflux surgery, who have successfully applied laparoscopic procedures in patients with all grades of oesophagitis[20,24,148].

An alternative tailored approach advocates modifying the type of fundoplication according to preoperative manometric variables[27,142]. Advocates of this approach would perform a partial rather than a Nissen fundoplication in patients with preoperative motility disturbances. However, there is no evidence from controlled trials to support this proposal. Other studies suggest that a loose Nissen fundoplication may produce equally good outcomes in patients with poor motility[149].

Short oesophagus

The incidence of oesophageal shortening found at antireflux surgery is controversial. Most surgeons report a very low likelihood of shortened oesophagus during laparoscopic antireflux surgery, with an incidence of conversion to an open procedure because of this problem at less than 1 per cent[21]. Although this suggests that the problem is infrequent, some argue that the ability of surgeons to determine adequate oesophageal length at the time of laparoscopic antireflux surgery is limited, and that the problem is more common than is usually appreciated[71,150]. Whether this is correct is uncertain. In the light of this, Kauer *et al.*[71] advocate an open transthoracic approach to perform a Collis gastroplasty in patients with a hiatal hernia length of more than 5 cm. Swanstrom *et al.*[150] recently described a method for the laparoscopic construction of a Collis gastroplasty; this offers an alternative solution for laparoscopic surgeons who encounter patients with a shortened oesophagus.

Conclusion

The promising early outcome studies for laparoscopic antireflux surgery are now supported by the initial results of randomized trials, confirming that this approach reduces the early morbidity of surgery for gastro-oesophageal reflux. Further medium-term outcome studies also confirm that the laparoscopic method controls pathological reflux as effectively as the traditional open operation. To achieve good results, however, surgeons should be aware of the potential for certain complications which are commoner following laparoscopic surgery and the need to adopt strategies to avoid them.

Currently published outcome studies and previous trials do not support the routine or selective application of a posterior partial fundoplication technique or routine division of the short gastric vessels. At present, a short loose Nissen fundoplication performed laparoscopically, with or without division of the short gastric vessels, is an appropriate surgical treatment for gastro-oesophageal reflux disease. However, long-term outcomes following laparoscopic antireflux surgery will not be available for some years; these must be awaited before the final status of the various laparoscopic techniques can be confirmed. In the meantime, the large clinical caseload that is now commonplace in many surgical departments should provide an opportunity for clinical trials to determine more fully the optimal approach for antireflux surgery.

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Review

Co-existing abdominal aortic aneurysm and intra-abdominal malignancy: reflections on the order of treatment

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Background The management of simultaneously occurring abdominal aortic aneurysm and intra-abdominal malignancy is controversial. It is unclear whether to treat the aneurysm first or the malignancy, or both simultaneously. If the malignancy is resected first there is a risk of postoperative rupture of the aneurysm. If simultaneous surgery is performed there is a risk of prosthetic graft infection from contamination by gastrointestinal or urinary tract contents.

Methods Relevant papers from 1960 to 1996, identified from Medline and manual searching, were reviewed.

Results and conclusion The literature supports the conclusion that the lesion of greater priority is that posing the greater threat to the patient; this is usually the aneurysm, especially if it is over 6 cm in diameter. For renal malignancies simultaneous surgery is the treatment of choice, but for bladder cancer the best management is unclear. Large aneurysms should usually be resected in preference to colorectal cancer unless the cancer is locally advanced, perforated or likely to result in early intestinal obstruction. If both lesions are complicated there may be a case for simultaneous treatment.

The concomitant occurrence of abdominal aortic aneurysm (AAA) and an abdominal malignancy represents a therapeutic dilemma. The main controversy revolves around whether to treat the lesions simultaneously or as staged procedures. If a staged approach is used which lesion should be dealt with first? Should a symptomatic lesion be treated first? Often both lesions are asymptomatic and the second lesion is only discovered at an operation for the initially recognized lesion.

Simultaneous treatment has the advantage of avoiding a second general anaesthetic but it increases the magnitude of the operation considerably. Traditionally, AAA treatment by insertion of a prosthetic graft has been avoided when there is potential for contamination from gastrointestinal or urinary tract contents, but evidence exists supporting simultaneous surgery. Ochsner *et al.*[1] showed that non-vascular operations may be performed at the same time as AAA repair without an increase in postoperative morbidity or mortality rate, and without an increase in graft infection. The commonest non-vascular operation performed simultaneously with AAA repair is appendicectomy, followed by cholecystectomy, lumbar sympathectomy, gastric resection, various herniorrhaphies and subtotal colectomy[1]. Stoll[2] reported seven cases of aneurysm repair performed concomitantly with other procedures including abdominoperineal resection, cholecystectomy and hiatal hernia repair. One patient underwent simultaneous aneurysm repair, cholecystectomy and abdominoperineal resection. There were no deaths and only one complication in a patient who required revision of a colostomy because of probable thrombosis of the middle colic artery. Other authors have also suggested that cholecystectomy may be performed safely at the same time as aneurysm repair provided that the retroperitoneum is closed before the gallbladder is removed[3–6]. Tompkins *et al.*[7] reported a series of 22 patients who underwent abdominal aortic surgery and a simultaneous non-vascular procedure including cholecystectomy, appendicectomy, vagotomy and drainage or gastrostomy. They concluded that necessary procedures could be safely performed concomitantly with aortic surgery.

In contrast, other authors have found an increased rate of complications when a non-vascular procedure is performed concomitantly with aortic surgery[8–11]. Connolly[12] reviewed the management of gastrointestinal and biliary tract lesions during aortic surgery and found that simultaneous cholecystectomy and aortic grafting is probably safe provided that the retroperitoneum is closed first. Nevertheless he also recommended that concomitant bowel resection should usually be avoided if possible. Thomas[13] reviewed the literature and his own experience, and found that most authors advised against opening a hollow viscus during aneurysm surgery, although this must be weighed carefully against the risk of postoperative aneurysm rupture if its repair is deferred. When the procedures are staged then there is the additional risk and possible complications of another operation. Furthermore, the complications of the first operation may postpone the second operation, resulting in a delay in definitive treatment for a potentially life-threatening condition.

A further consideration is that laparotomy for an unrelated condition seems to increase the risk of AAA rupture in the immediate postoperative period. Swanson *et al.*[14] reported that previously asymptomatic aneurysms in ten patients ruptured within 36 days of a laparotomy. All but one of these aneurysms were greater than 6 cm in size. The mechanism for this is poorly understood but these authors speculated that laparotomy may have precipitated rupture by somehow reducing the collagen content of the aneurysm wall, thus weakening the wall. No evidence exists for this theory. Trueblood *et al.*[15] described

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17 patients with AAA who underwent unrelated surgery of whom four died in the immediate postoperative period from aneurysm rupture, representing a 24 per cent mortality rate for unrelated elective operation in patients with known AAA. These authors believed that operative manipulation and trauma were the only common features of the cases.

The reported incidence of concomitant AAA and malignancy varies but is not high. Nora *et al.*[16] found that of a series of 3500 AAAs repaired at the Mayo Clinic over a 12-year period there were only 17 associated with a colorectal malignancy, an incidence of 0·5 per cent. Robinson *et al.*[17] reported that over a 10-year period 1337 aneurysms were treated of which 19 were associated with a concomitant colorectal malignancy, an incidence of 1·4 per cent. The incidence was possibly higher in the latter study because it included aneurysms treated non-operatively. Morris and Colquitt[18] reviewed the records of 158 patients with aneurysm who presented over a 12-year period and found that 20 had a histologically proven malignancy, an incidence of 12·7 per cent. The incidence in this series is high first because it includes AAA treated non-operatively and, second, because it includes all malignancies. Finally, in this series the aneurysm and the malignancy were not necessarily diagnosed simultaneously. The commonest malignancies were prostatic (eight patients; incidence 5·1 per cent), colorectal (six patients; incidence 3·8 per cent), lung (three patients; incidence 1·9 per cent) and one each of pancreas, breast and unknown primary.

Szilagyi *et al.*[19] found the combined incidence of all malignancies with all AAAs treated was 3·9 per cent; the incidence of prostatic cancer with an aneurysm was 0·2 per cent, colorectal cancer 1·2 per cent and lung cancer 1·0 per cent. Szilagyi's review included patients with renal, pancreatic and gastric malignancies as well as metastatic adenocarcinoma of the liver and ileal carcinoid.

For this review a literature search was performed for all papers dealing with the management of concomitant AAA and intra-abdominal malignancy from 1960 to 1996. Both Medline and manual searching were used. It should be stated here that the quality of evidence provided in the literature is poor and that there is a lack of randomized trials or cohort studies.

Concomitant urological malignancies

The increasing use of ultrasonography and computed tomography (CT) for screening and detection of AAA has also led to the detection of other intra-abdominal conditions, particularly renal malignancies[20]. Aneurysm may be associated with a variety of urological malignancies including renal cell carcinoma and transitional cell carcinoma (TCC) of the renal tract, including bladder and prostate adenocarcinoma.

Renal carcinoma

In 1996 Konety *et al.*[20] reported the retrospective results of ten patients who underwent aneurysm repair and combined radical nephrectomy. They compared the outcome with that of another ten patients who underwent radical nephrectomy alone and that of 12 patients who had aneurysm repair alone. Of the ten patients with co-existing lesions, in eight the renal mass was discovered only during CT for investigation for AAA. In the remaining two the aneurysm was found during investigation for haematuria. The authors found no significant differences in outcome between the test and control groups and, in particular, there were no graft infections. They concluded that simultaneous cancer resection and aneurysm repair was safe in suitable patients and had the advantages of avoiding a second general anaesthetic and the risk of postoperative aneurysm rupture. Criticisms of this study include the lack of a proper control group. It would have been more satisfactory if patients undergoing simultaneous procedures were compared with those having staged operations for co-existing lesions, although no doubt lack of adequate numbers would have made this difficult. It was unclear from the study what criteria were used to determine the management plan for particular patients.

The conclusions of Konety *et al.*[20] are supported by DeMasi *et al.*[21] who presented six patients with co-existing AAA and renal carcinoma. Four aneurysms were treated simultaneously with nephrectomy, a fifth case was managed by nephrectomy followed by interval aneurysm repair and the sixth patient was treated conservatively because of metastatic disease. There were no vascular complications but two patients died, one from a stroke following combined procedures and the other from an unknown cause. In this study a retroperitoneal approach was used for the AAA if the renal tumour was on the left side and transperitoneal if on the right. Konety *et al.*[20] used a transperitoneal approach except in one case of massive renal tumour for which a thoracoabdominal incision was employed. Baskin *et al.*[22] also reported a case of simultaneous repair of an aneurysm and resection of renal clear carcinoma through a transperitoneal approach, with successful outcome.

Transitional cell carcinoma of the bladder

Management of concomitant TCC of the bladder and AAA presents more formidable technical challenges than those associated with concomitant renal tumours. Lierz *et al.*[23] presented eight patients with synchronous aneurysm and invasive bladder cancer, all of whom either underwent staged surgery or were managed conservatively because of metastatic disease. All deaths were related to malignancy or cardiac complications and none were due to aneurysm rupture or other vascular problems. Lierz *et al.*[23] ruled out simultaneous aneurysm repair and cystectomy because of the technical difficulty, and potential for graft infection from spilled urine and bowel content. Initial tumour resection was not a favoured option because of the risk of aneurysm rupture in the postoperative period, although this did not occur in the small number of patients in their study. It must also be appreciated that subsequent aneurysm repair after cystectomy and urinary diversion risks direct trauma or vascular compromise of the ureters and conduit used for the diversion. Thus Lierz *et al.*[23] favoured aneurysm repair before staged cystectomy, even though this risks further tumour growth during the interval between operations in a patient weakened by a major procedure. While this continuing tumour growth after aneurysm repair may not be clinically significant, the risk of graft infection remains at the second operation if the prosthesis has not been completely sealed by fibrosis. Among the technical difficulties encountered was that of performing a pelvic node dissection when there had been a recent aneurysm repair. These workers therefore favour node dissection at the same time as the AAA repair.

Ginsberg *et al.*[24] criticized the two-stage approach for resection of TCC of the bladder because it involves two major procedures within a short period of time and because the second operation may be made excessively difficult by intra-abdominal adhesions from the first operation. The avoidance of graft contamination in a staged approach may not compensate for these disadvantages. They subjected 12 patients with TCC of the renal tract and AAA to simultaneous surgery and did not have any vascular or urological complications. Five patients underwent aneurysm repair with or without node dissection and subsequent staged urological resection. The authors found the urological resection to be complicated by retroperitoneal fibrosis, and there were two urological complications, a urinary leak and a devascularized ureter. Ginsberg *et al.*[24] therefore found a staged approach unsatisfactory, mainly because of the difficulty of ureteral dissection at the second operation, but emphasized the need for thorough bowel preparation and perioperative antibiotics. Both Lierz *et al.*[23] and Ginsberg and coworkers[24] accept that the aneurysm deserves higher priority than the urological malignancy, partly because it poses the greatest threat (at least if it is over 5–6 cm in diameter) and partly because of the known high incidence of postoperative aneurysmal rupture[15].

It is difficult to assess the relevance of the studies of Lierz and colleagues[23] and Ginsberg *et al.*[24] because of the lack of a treatment protocol. The reasons for choosing each of the management options for any particular patient were not defined. The former group recommend staged surgery with aneurysm repair first, but they have not actually compared different management options. Many of the patients in their study did not complete the planned treatment because of metastatic disease or because of refusal to undergo a second operation. Ginsberg *et al.*[24] did compare patients undergoing a combined operation with those having aneurysm repair followed by staged urological resection. There did seem to be technical advantages to a combined operation but the number of patients was small and it is difficult to draw a firm conclusion.

Colorectal cancer

Management of co-existing AAA and colorectal malignancy causes the greatest dilemma as there is no clear consensus on whether to treat the cancer or the aneurysm first, or indeed simultaneously. Lobbato *et al.*[25] wrote to 46 professors of general or vascular surgery to obtain their opinion as to which condition should receive priority of treatment. Of 23 professors of general surgery seven would perform colectomy first, seven would perform aneurysm repair first, eight would withhold a decision until laparotomy was performed and one would perform both procedures simultaneously. Of the 16 professors of vascular surgery five would perform colectomy first, seven would perform aneurysm repair first and four would wait for laparotomy to make a decision. Of the seven who were chairmen of both departments, two would perform colectomy first, two would do aneurysm repair first, two would wait for laparotomy and one would carry out simultaneous procedures.

Therefore 14 of 46 professors preferred cancer resection initially but qualified their answers by assuming that the bowel was prepared, the tumour was causing actual or imminent obstruction and that the aneurysm was not large. Sixteen professors preferred aneurysm resection initially but assumed that the aneurysm was large and the tumour was not causing complications. Fourteen of the respondents would wait for laparotomy and mentioned similar important factors to those already described above. Only two would perform simultaneous procedures and both stated that both lesions would have to be uncomplicated.

Nora *et al.*[16] reviewed the records of 17 patients with concomitant colorectal cancer and AAA at the Mayo Clinic. Surgical chronological preference was determined by presence of malignant spread, presence of symptoms and personal preference. In most cases the cancer was resected first and this may have been due to the fact that most patients presented with symptoms of malignancy rather than of aneurysm. One patient had aneurysm repair alone, one had aneurysm repair followed by staged cancer resection, two had simultaneous surgery, five had cancer resection followed by staged aneurysm repair and eight had cancer resection only. There were only four long-term survivors (alive at the time of the study, 18 months to 4 years after treatment) all of whom had both lesions treated. Three patients who had cancer resected initially died from ruptured AAA in the postoperative period at 5 weeks, 6 weeks and 3 months. The long-term results were discouraging and most patients died from metastatic disease or complications of untreated AAA (rupture or thrombosis of aneurysm). The six patients who died from metastatic disease survived from 6 months to 3·5 years after surgery. For long-term survival it seems necessary to treat both lesions and in this study the authors admitted that a more aggressive approach to the aneurysm was warranted.

Robinson *et al.*[17] presented a retrospective series of 19 patients with co-existing AAA and colorectal cancer. Twelve patients had the cancer resected but the aneurysm left, and two of them died from postoperative rupture at 5 days (6-cm aneurysm) and 8 months (10-cm aneurysm). Five patients had the cancer resected and delayed aneurysm repair, and two patients underwent simultaneous procedures. The overall prognosis was again poor with only five long-term survivors, of whom three had undergone surgery for both lesions and two had only small aneurysms. The long-term survivors were alive at between 4 months and 9·5 years of follow-up; the patients with metastatic disease survived from 2 months to 1·8 years. It was unclear how the priority of treatment for individual patients was decided, although the reasons for non-operative treatment of aneurysm included the presence of metastatic disease, patient unfitness for major surgery and small aneurysm size (4 cm or less).

Velanovich and Andersen[26] applied decision analysis techniques to quantify the risk : benefit ratio involved in assessing priority of treatment. Important factors in determining priority of treatment included rate of aneurysm rupture, rate of graft infection and rate of complications caused by the cancer. The most difficult factor to quantify was the probability of a particular cancer causing complications such as obstruction or perforation. It seems reasonable to assume that small cancers have an associated low risk and larger, perhaps circumferential cancers, a higher risk of complications. However, this is rather inexact and further uncertainties arise from the lack of information available on the natural history of patients with co-existing AAA and colonic cancer; there is also little known about aortic graft infection rates when associated with colonic resection. Velanovich and

Andersen[26] concluded that when both lesions are asymptomatic an aneurysm of less than 5 cm diameter should be treated first if the cancer has a less than 5 per cent chance of causing complications. If the aneurysm is more than 5 cm in diameter it should be repaired first if the cancer has a less than 20–25 per cent of causing complications. Simultaneous procedures should be considered if the aneurysm is more than 5 cm in diameter and the cancer has a more than 75–80 per cent chance of obstruction or perforation, provided that the operative mortality rate is likely to be less than 10 per cent. There are no specific figures given for cancer resection followed by aneurysm repair. The outcome of such a scenario would depend on aneurysm size and the postoperative rupture rate, as well as the graft infection rate after colonic surgery, which would be difficult to quantify.

There is little in the literature regarding simultaneous operation for colonic cancer and AAA. Nora *et al.*[16] managed two patients with simultaneous surgery and both survived the postoperative period with one alive at 18 months and the other surviving for 12 months until metastases intervened. Gouny *et al.*[27] reported two cases of concomitant aneurysm and colonic cancer managed by simultaneous procedures. One patient was alive at 15 months' follow-up and the other died after 20 months from metastatic disease. There was no graft infection in either patient. Simultaneous surgery has many theoretical attractions including avoiding complications relating to the unresected lesion, avoiding a second operation and allowing definitive treatment of both lesions. It is common when the operations are staged for the second procedure to be delayed either by complications or by the patient's refusal to undergo further major surgery[16]. It seems clear from the available studies[15,16] that only the treatment of both lesions, either simultaneously or staged, offers a chance of long-term survival. While Gouny *et al.*[27] recommend that two-stage treatment should be the usual choice to reduce the risk of graft infection, it is possible that single-stage treatment may be necessary if both lesions are complicated[26].

Discussion

While co-existing AAA and intra-abdominal malignancy is not a common problem, it presents a challenging dilemma of management. When the vascular surgeon discovers intra-abdominal malignancy before or during laparotomy the main considerations are to treat both lesions effectively, and to minimize the risks of graft infection and of postoperative rupture of the aneurysm[13]. The particular arguments about whether to perform a simultaneous or a staged operation depend on the type of malignancy. Probably the least controversial type of malignancy is renal, for which simultaneous treatment is probably the method of choice. Both Konety *et al.*[20] and DeMasi and colleagues[21] have shown that combined surgery carries no greater risk than staged surgery in suitable patients. A more conservative approach may be advisable in those of advanced age or with preoperative renal dysfunction, or when the aneurysm is complicated or symptomatic. A nephrectomy carries little if any risk of intraoperative contamination from urine or of postoperative leakage; the feared complication of graft infection is, therefore, unlikely to occur[20].

This consideration does not apply to invasive bladder carcinoma for which cystectomy and urinary diversion provide the potential for contamination from urinary tract and bowel content. Simultaneous surgery, as advocated by Ginsberg *et al.*[24], avoids a second operation which is made more difficult by intra-abdominal adhesions and a retroperitoneal desmoplastic reaction, but it risks graft infection. In contrast Lierz *et al.*[23] recommend a staged approach in which the aneurysm is resected first provided it is over 5 cm in diameter and is followed by a cystectomy. This reduces the risk of postoperative rupture and also of graft infection. Disadvantages include a second major operation and the difficulty of ureteral dissection at the subsequent cystectomy. On the basis of current evidence, which depends on only a small number of patients, a simultaneous procedure has no particular advantage over staged treatment.

The management of patients with colorectal cancer and AAA also remains controversial. This is illustrated by the response to questionnaires from general and vascular surgeons as found by Lobbato *et al.*[25]. The incidence of co-existing AAA and colorectal cancer ranges from 0·49 per cent[16] to 1·4 per cent. Probably the most reliable estimate of the true incidence is that of Nora *et al.*[16] whose series of 3500 aneurysms actually repaired contained 17 patients with simultaneous colorectal carcinoma. The discrepancy in incidence between the various studies probably depends on whether all aneurysms are included or just those operated on, and also whether only simultaneously diagnosed malignancies are included or all malignancies associated with a patient with an AAA. In the UK in 1995 there were approximately 7000 elective and emergency operations for AAA[28], giving an estimated annual incidence of concomitant colorectal malignancy of between 35 and 105. Many of the studies on the subject again involve small numbers and are difficult to interpret. Szilagyi *et al.*[19], in their original review, recommended that the symptomatic lesion should be treated first; for the colorectal malignancy symptomatic means perforation or obstruction. If both lesions are asymptomatic then priority should be given to the aneurysm if it is large and the cancer if the aneurysm is small. This recommendation is based on the poor results achieved when patients with co-existing lesions have colon resection first, since they have a tendency to die from complications of their untreated aneurysm[13–17,19,26].

Rupture of AAA after an unrelated abdominal procedure has been well described[14,15] and seems to vary in incidence between 16 per cent[17] and 24 per cent[15]. The mechanism was originally believed to be related to increased collagen lysis[14], although in animal studies neither laparotomy nor bowel resection affects aortic collagenase activity[29]. It is possible that the size and degree of surgical exposure of the aneurysm are more important factors in postoperative rupture[29].

The outcome for patients who have undergone concomitant surgery for colorectal cancer and AAA is not well documented. Simultaneous surgery removes the risk of a second major operation and the risk of complications of the untreated lesion, but the risk of graft infection remains. Patients in two significant series[16,27] had a favourable outcome with this management option, although long-term survival was only 24 per cent in these fairly small groups of patients.

Infection involving an aortic reconstruction operation is a disastrous complication requiring complex and radical surgery if there is to be any chance of avoiding a fatal outcome[30,31]. It is significant that although *Staphylococcus aureus* is the commonest organism infecting vascular grafts, Lorentzen *et al.*[31] found that *Streptococcus faecalis* is responsible for no less than 14·5 per cent of infections. Leikweg and Greenfield[32] showed that 40 per cent of graft infections were caused by Gram-negative organisms. Becker and Blundell[33] reported 14 cases of infected aortic bifurcation grafts of which two were attributed to concomitant cholecystectomy and one to concomitant gastrostomy. Ouriel *et al.*[3] described one graft infection following simultaneous AAA repair and cholecystectomy. Whatever the predisposing factors contributing to prosthetic graft infection, the mortality rate associated with such infection is high: 65 per cent in Bernhard's[33] series of 20 patients with infected grafts following AAA repair, and 46 per cent in the series of Leikweg and Greenfield[32] which contained 11 cases of infected grafts in the aortoiliofemoral region. Szilagyi *et al.*[34] found the incidence of graft infection for aortoiliac reconstruction to be 0·7 per cent, whereas it rose to 1·6 per cent when a groin incision was used as in aortobifemoral bypass. *Staphylococcus* was the usual pathogen when the infection originated in the groin. *Escherichia coli* predominated in infected aortoiliac grafts (five cases), where the source of infection was a perforated hollow viscus.

The degree of tumour control at the time of diagnosis of the aneurysm has an obvious bearing on management. In the presence of metastases a more conservative approach is warranted. As Morris and Colquitt[18] note, the type of cancer is also relevant; for instance patients with metastatic prostate cancer may be better candidates for aneurysm repair than those with metastatic lung cancer. Szilagyi *et al.*[19] recommend that if metastases are present an AAA should only be repaired if it is symptomatic or of large size (exceeding 6 cm), with the malignancy under good albeit temporary control and the patient a good operative risk. Nora *et al.*[16] found that patients with metastases may survive up to 3·5 years, and it may be that such patients occasionally benefit from aneurysm repair.

Finally, the quality of the evidence reviewed here is poor, consisting of retrospective studies of small numbers of patients without proper controls. It is not possible to produce clear guidelines on the management of patients with concomitant aneurysms and intra-abdominal malignancy. The following are the authors' own conclusions.

Conclusions

1. Combined AAA repair and nephrectomy carries no increased risk compared with staged procedures, provided that the patient is not of advanced age or with significantly impaired renal function.
2. For concomitant bladder malignancy, simultaneous or staged operation involves technical difficulties and the risk of graft infection.
3. For concomitant colorectal cancer, the lesion of higher treatment priority is that posing the greater immediate threat to the patient. It is probable that the aneurysm, especially if more than 5–6 cm in diameter, will usually pose the greater threat.
4. There is no clear evidence that a short delay caused by aneurysm surgery adversely affects the cancer prognosis.
5. It is possible that a recent colorectal resection predisposes to graft infection, although there is no evidence to support this.
6. If the cancer is resected first there is an increased risk of AAA rupture in the immediate postoperative period.
7. Large aneurysms should usually be resected in preference to colorectal cancer unless the cancer is locally advanced, perforated or likely to result in early intestinal obstruction. What constitutes a large aneurysm in this context is unknown, but would probably be in excess of 5–6 cm diameter.

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Review

Chlamydia pneumoniae and vascular disease

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Background There is an increasing body of evidence linking the human pathogen *Chlamydia pneumoniae* with atherosclerosis.

Methods A Medline-based review of the literature was carried out.

Results and conclusion Seroepidemiological studies have revealed the possibility that evidence of infection with *C. pneumoniae* and atherosclerotic disease are related. Studies on human tissue have demonstrated that evidence of the organism can be found in human atherosclerotic tissue by both direct and indirect methods significantly more often than in control vascular tissue. Using animal models it is possible to show that *C. pneumoniae* can be disseminated haematogenously following pulmonary infection and that it shows a tropism for atherosclerotic tissue. *In vitro* work has demonstrated that the organism is capable of infecting, surviving and multiplying in cells of the human vascular wall, and that it can provoke a cell-mediated cytokine response which has implications both locally and systemically. Two clinical trials of macrolide antibiotics have demonstrated that they confer increased cardiovascular protection in patients following myocardial infarction. Adequately powered trials are needed to establish the therapeutic role of antibiotics in peripheral arterial disease.

Chlamydia are Gram-negative obligatory intracellular bacteria responsible for a wide range of chronic, progressive inflammatory conditions. These include trachoma leading to blindness[1] and genital infection[2] associated with pelvic inflammatory disease, ectopic pregnancy and infertility (*C. trachomatis*), human pneumonitis[3] (*C. psittaci*) and respiratory tract infection (*C. pneumoniae*)[4]. The outer cell membrane of the genus consists of lipopolysaccharide (LPS), which is antigenically genus specific. The LPS contains outer membrane proteins which are species specific[5]. The organism has a biphasic life cycle, with an infectious elementary body (EB), which can survive extracellularly and which is transmitted between humans via aerosol drops. The EB attaches to the host cell surface and is phagocytosed by the lining epithelium. The EB then differentiates intracellularly into the metabolically active reticulate body (RB), which replicates by binary fission to form inclusion bodies in the cell. The RBs differentiate into EBs over the next 40–72 h, with subsequent lysis of the infected cell which releases the new EBs and initiates the next replicative cycle[6]. *C. pneumoniae* was first identified 11 years ago[7] and has been recognized as an important cause of respiratory tract infections in the community including pneumonia, pharyingitis and bronchitis. Infection is asymptomatic or causes only mild symptoms, and is both epidemic and endemic. Epidemics of *C. pneumoniae* occur every 5–7 years and it is estimated that between 50 and 70 per cent of adults are seropositive, with primary infection occurring in teenage years and prevalence rising with age[8]. Cycles of reinfection are common[9]. There has been increasing recent attention paid to the possible role of *C. pneumoniae* in atherosclerosis.

Seroepidemiology

C. pneumoniae was first associated with coronary arterial disease when Finnish investigators in a small observational study demonstrated that raised titres of immunoglobulin (Ig) G and IgA antibodies to *C. pneumoniae* were present in 68 per cent of men after acute myocardial infarction (40 cases) and 50 per cent of men with chronic coronary heart disease (30 cases); this compared to 17 per cent of age-matched healthy controls[10]. The study did not adjust for important risk factors for atherosclerosis, such as smoking[11].

The same group, using 103 sera collected prospectively from patients in the Helsinki Heart Study, demonstrated in a nested case–control study of patients who subsequently underwent a cardiac event 3–6 months later, that the risk of coronary disease for those with raised titres of antibodies was twice that of controls; this was independent of other confounding factors such as age and smoking[12]. The presence of raised levels of IgA antibodies to *C. pneumoniae,* together with circulating immune complexes containing chlamydial LPS, constituted the strongest risk factor (times 2·6) for development of subsequent coronary artery disease. A further significant association between circulating *C. pneumoniae*-specific immune complexes and chronic coronary arterial disease was demonstrated in 19 (41 per cent) of 46 patients with angiographically proven coronary artery disease compared with 15 per cent of age- and sex-matched controls[13].

Mendall *et al.*[14] showed that 22 per cent of 100 men with angiographically proven coronary artery disease had raised titres of IgG antibody to *C. pneumoniae,* compared with only 4·7 per cent of age-matched controls. At titres above 1 : 64 the IgG association with disease was independent of all other risk factors. Among the healthy controls the only significant risk factor for raised titres of IgG was the number of children living in the home at the

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time, potentially acting as a source of infection. In a larger cross-sectional study of 388 men there was again a significant association between raised IgG to *C. pneumoniae* and coronary arterial disease as demonstrated by an abnormal electrocardiogram (odds ratio 3·06) after adjustment for potential confounding factors. Seropositivity to *C. pneumoniae* was independently associated with raised fibrinogen level, a cardiovascular risk factor[15]. Further cross-sectional studies involving 171–326 subjects have shown a similar association of raised titres of IgG antibodies against *C. pneumoniae* with coronary artery disease[16] and asymptomatic carotid wall thickening[17] (adjusted odds ratios of 4·2 and 2·00 respectively for an association between presence of antibody and atherosclerosis after controlling for known risk factors). Chronic infection, demonstrated by raised levels of IgA antibodies and IgG-specific circulating immune complexes to *C. pneumoniae*, have also been shown to be associated with an increased risk of transient ischaemic attack and stroke in 58 subjects under the age of 50 years with age-matched controls[18].

Detection of *Chlamydia pneumoniae* in cardiovascular tissue

On the basis of the seroepidemiological association between *C. pneumoniae* and coronary artery disease, evidence of the presence of the organism in atherosclerotic lesions was the next step for investigators. This was achieved by Shor *et al.*[19] in 1992. These workers identified the EBs of *C. pneumoniae* by electron microscopy in the fatty streaks and plaques of post-mortem coronary arteries of young adult men; species specificity was confirmed by immunostaining. There have been a total of 17 reports in the literature to date of identification of *C. pneumoniae* in cardiovascular lesions[19–35]. A variety of techniques have been used, including the polymerase chain reaction (PCR), immunocytochemical staining (ICC), immunofluorescence, *in situ* hybridization and (once) direct culture of the organism[29] (*Table 1*). Fifteen of these papers examined the prevalence of *C. pneumoniae* in atherosclerotic arterial lesions ($n = 597$), with 11 of them making comparison with non-atherosclerotic controls ($n = 131$). Summation analysis demonstrates that there was a highly significant difference between the two groups, with 303 (50·8 per cent) of the atherosclerotic arterial specimens positive for *C. pneumoniae* against five (3·8 per cent) of the control tissues. A wide range of detection rates exists between both different investigators and different techniques, with one paper claiming 100 per cent detection using PCR[30] while another found only one of 56 specimens weakly positive using the same technique[26]. Evidence of *C. pneumoniae* can be found not only in atherosclerotic arterial tissue; it has also been identified in iliac veins[25], stenotic aortic valves[31] and, in a comparison of the prevalence of the organism in cardiovascular against non-cardiovascular tissue, it was present in both venous bypass grafts and myocardium[32]. The organism may be detected throughout the arterial tree; eight of the reports concern coronary artery specimens, four aorta, three carotid and two infrainguinal arteries.

Electron microscopy (EM) and double ICC staining of specimens has shown that the organism is located in the central necrotic core and cholesterol clefts of the atherosclerotic plaque[19,20,30]. It has been demonstrated in the whole thickness of the plaque, particularly in the subendothelium[21]. The organism has been reported both in interstitial tissue[27] and within macrophages, foam cells and smooth muscle cells[22,30,33]. Its demonstration was more likely in atheroma with a moderate to severe inflammatory infiltrate[25], and could not be shown in adjacent normal vessel wall[20,35].

Markers of infection

The association between seropositivity to *C. pneumoniae* and atherosclerotic arterial disease has been demonstrated on a population basis, thus potentially enabling raised titres of antibodies to be used as a marker for patients with *C. pneumoniae* present in their atheroma. This would provide a means of identifying patients suitable for prospective trials to determine whether intervention (i.e. antibiotics) could modify or alter disease progression. However, the literature suggests that, for individuals, seropositivity is of no value in distinguishing the presence of *C. pneumoniae* in atheroma. Kuo *et al.*[20] found in their series that the six patients with the highest titres of serum IgG had no evidence of *C. pneumoniae* in their atheromatous lesions, while six of eight patients with no detectable IgG did have evidence of *C. pneumoniae* in the atheroma. This leads to speculation that a raised serum IgG level conferred protection against *C. pneumoniae* in atheromatous lesions, despite the original seroepidemiological evidence. Weiss *et al.*[26] found that IgG titres were more likely to be positive in 28 control patients than in 65 patients undergoing coronary atherectomy. Other studies have similarly found seropositivity to be of no value in predicting which lesions will have evidence of *C. pneumoniae*[23,28,33,34].

Research is currently being undertaken to identify a marker of *C. pneumoniae* involvement in arterial lesions. Specific antigens of *C. pneumoniae* recognized by immunoblotting have been associated with increased risk of cardiovascular disease[36]. *C. pneumoniae* has been identified in both atheroma and circulating monocytes[37], and *C. pneumoniae* DNA has been detected in the sera of patients and controls using PCR, with positivity occurring more frequently in patients with coronary arterial disease (48 per cent) and acute myocardial infarction (25 per cent) than in the control group (12 per cent). Positivity increased in all three groups with antibody response[38].

Mechanisms of damage

Evidence of *C. pneumoniae* in the atherosclerotic lesion is not evidence that the organism plays a causal or disease modifying role. It might simply seed in atheroma following a respiratory infection and remain there inert as an 'innocent bystander'. However, it is also possible that *C. pneumoniae* acts in common with other chlamydial species to cause chronic inflammation leading to the development of clinical disease 10–50 years after the primary infection[8].

To play a pathogenic role in atherosclerosis the organism must first gain entry to the cells of the arterial wall. This has been demonstrated in an animal model; following single intranasal and tracheal inoculation with *C. pneumoniae*, hereditary hyperlipidaemic rabbits develop an interstitial pneumonia. The organism can be detected in peripheral monocytes 3 days after inoculation and in splenic tissue 2 weeks later, suggesting haematogenous dissemination of the organism following initial

Table 1 Detection of *C. pneumoniae* in human cardiovascular tissue

Reference	Year	Tissue type	No.	Detection technique						No. positive (%)
				PCR	ICC	EM	DC	IF	IS	
Shor *et al.*[19]	1992	PM CA fatty streaks/plaques	7		5 of 7	7 of 7				5 of 7 (71)
		Controls: PM non-diseased CA	5		0 of 5					0 of 5 (0)
Kuo *et al.*[20]	1993	PM CA atheroma	36	13 of 30	15 of 36	6 of 21				20 of 36 (56)
		Controls: PM non-diseased CA	11	0 of 6	0 of 11					0 of 11 (0)
Kuo *et al.*[21]	1993	PM aortic atheroma	21		7 of 21					6 of 20 (30)
		Controls: PM normal aorta	4		0 of 4					0 of 4 (0)
Kuo *et al.*[22]	1995	PM CA < 34 years	49	3 of 49	7 of 49					
		Atheromatous	18	3 of 18	7 of 18					8 of 18 (44)
		Non-diseased	31	0	0					0 of 31 (0)
Campbell *et al.*[23]	1995	CA atherectomy tissue	38	12 of 38	17 of 38					20 of 38 (53)
Grayston *et al.*[24]	1995	CEA tissue	5 fresh	2 of 3	5 of 5					37 of 61 (61)
			56 formalin	1 of 2	31 of 56					
		Controls: PM carotid artery	6		0 of 6					0 of 6 (0)
Ong *et al.*[25]	1996	Aortic and PA atheroma	35	15 of 35				3 of 12		15 of 35 (43)
		Control: vascular tissue from transplant donors	8	4 of 8						4 of 8 (50)
Weiss *et al.*[26]	1996	CA atherectomy tissue	58	1 of 56		0 of 2	0 of 58			1 of 58 (2)
Muhlestein *et al.*[27]	1996	CA atherectomy tissue	90			3 of 5		71 of 90		71 of 90 (79)
		CA controls: non-atherosclerotic	24					1 of 24		1 of 24 (4)
Blasi *et al.*[28]	1996	AAA tissue	51	26 of 51						26 of 51 (51)
Ramirez[29]	1996	CA from cardiac explants	12							
		Atheromatous	10	3 of 10	5 of 10	3 of 10	1 of 10		1 of 10	7 of 10 (70)
		Non-atheromatous	2	0 of 2	0 of 2	0 of 2				0 of 2 (0)
Juvonen *et al.*[30]	1997	AAA tissue	12	6 of 6	12 of 12	3 of 4	0 of 3			12 of 12 (100)
		Controls: PM aortic tissue	3	0	0					0 of 12 (0)
		Punch biopsy ascending aortas	9	0	0					
Juvonen *et al.*[31]	1997	AV replacements	17	3 of 17	9 of 17	2 of 3				19 of 27 (70)
		PM diseased AV	10		8 of 10					
		Controls: PM normal AV	8		1 of 8					1 of 8 (12)
Jackson *et al.*[32]	1997	PM cardiovascular tissue	57	9 of 57	11 of 57					19 of 57 (33)
		PM non-vascular tissue	146	5 of 146	9 of 146					14 of 146 (9·6)
		Granulomas	33	2 of 33	1 of 33					3 of 33 (9)
Chiu *et al.*[33]	1997	CEA specimens	76		54 of 76					54 of 76 (71)
		Controls: PM carotid + aorta	20		0 of 20					0 of 20 (0)
Kuo *et al.*[34]	1997	PA atheroma	39	5 of 39	9 of 20		0 of 26			11 of 23 (48)
		Controls: non-diseased PA	8	0 of 8	0 of 8					0 of 8 (0)
Maass *et al.*[35]	1997	CEA specimens	61	9 of 61						9 of 61 (15)
		Macroscopically normal CEA tissue from same series	39	0 of 39						0 of 39 (0)

PCR, polymerase chain reaction; ICC, immunocytochemistry; EM, electron microscopy; DC, direct culture; IF, immunofluorescence; IS, *in situ* hybridization; PM, post mortem; CA, coronary artery; CEA, carotid endarterectomy; PA, peripheral artery; AAA, abdominal aortic aneurysm; AV, aortic valve pulmonary infection[39]. In a similar study New Zealand white rabbits also developed early and intermediate lesions of aortic atherosclerosis, in addition to lung inflammation, following inoculation; *C. pneumoniae* was demonstrated in one of the lesions[40].

Animal models have also suggested that the organism has a tropism for atherosclerotic lesions. After intranasal inoculation of *C. pneumoniae* apoprotein E-deficient mice, which spontaneously develop atherosclerosis, have persistent evidence of *C. pneumoniae* in developing aortic atheroma, unlike inoculated wild strain mice which do not develop atherosclerosis[41]. This predilection for atheroma by *C. pneumoniae* has also been described in human subjects[32]. *In vitro* work has shown that *C. pneumoniae* is capable of infecting, surviving and multiplying in endothelial cells, smooth muscle cells and macrophages, all constituents of the arterial wall[42,43].

The possible mechanisms by which *C. pneumoniae* mediates damage to the vascular system include the provocation of changes in the plasma and/or in the vessel wall. Infection is recognized as a risk factor in atherosclerotic disease such as myocardial infarction and stroke, possibly by inducing a hypercoagulable state which predisposes to thrombotic episodes[44]. Both serum fibrinogen[45] and C-reactive protein (CRP)[46] are associated with seropositivity to *C. pneumoniae*, and the organism has been shown *in vitro* to stimulate a fourfold increase in expression of tissue factor from infected human endothelial cells[47], which would increase the risk of thrombosis on the plaque.

It is postulated that the presence of *C. pneumoniae* or *C. pneumoniae* antigens within cells of the arterial wall acts as a stimulus to chronic inflammation. It is possible that the organism itself would not have to be viable to act as an immunogenic stimulus to inflammation and atherogenesis[6]. The cytokine response from endothelial and smooth muscle cells, as well from leucocytes, is felt to be an important mechanism in atherosclerosis-associated inflammation; the bacterial LPS antigen in particular is recognized as a potent stimulus to macrophage activation[48]. *C. pneumoniae* multiplying in human monocytes have been shown to induce production of cytokines as part of the cell-mediated immune response. These include tumour necrosis factor (TNF) α, interleukin (IL) 1β and IL-6[49,50], all of which mediate a range of effects both locally and systemically. Direct effects of TNF-α on vascular wall cells include increased expression of leucocyte adhesion molecules[51] and promotion of angiogenesis[52], whilst IL-1β and IL-6 both activate T cells. In the circulation these cytokines all promote a hypercoagulable state by activating platelets[53], increasing hepatic synthesis of acute-phase proteins (including fibrinogen)[54], stimulating endothelial procoagulant activity[55], and inducing tissue factor release from endothelium with subsequent activation of the coagulation cascade[56]. TNF-α increases circulating serum triglycerides and very low density lipoprotein concentrations, and decreases circulating levels of high density lipoprotein[57], producing a favourable environment for atherogenesis.

Clinical trials

The hypothesis that *C. pneumoniae* causes or contributes to inflammation in atherosclerosis had led to two clinical trials of antichlamydial macrolide antibiotics in patients with coronary artery atherosclerosis. Two hundred and twenty male survivors of myocardial infarction were tested for serum IgG antibodies against *C. pneumoniae* and placed into one of three groups based on antibody titres[58]. Those in the group with the highest levels (a serum dilution of one or more in 64) were retested at 3 months and, if the IgG response was persistent, they were randomized into a double-blind placebo-controlled study of azithromycin 500 mg daily for either 3 or 6 days, or placebo. Adverse cardiovascular events (non-fatal myocardial infarction, unstable angina requiring intravenous therapy, angioplasty or surgery, and cardiovascular death) were then monitored for 18 months from first IgG titre determination. The results showed that the frequency of adverse effects increased with rising anti-*C. pneumoniae* IgG levels (7 per cent in the seronegative group, 28 per cent in the untreated more than 1/64 group), and that there was a fivefold reduction in adverse events in patients receiving azithromycin compared with those receiving placebo, or those not entered ($P = 0{\cdot}03$). In the ROXIS (randomised trial of roxithromycin in non-Q-wave coronary syndromes) study[59] 202 patients with unstable angina or non-Q-wave myocardial infarction were randomized to roxithromycin 300 mg daily or placebo. Further cardiac events (recurrent angina, acute myocardial infarction or death) were reduced from 10 per cent in the placebo group to 1 per cent in the roxithromycin group ($P = 0{\cdot}018$).

The findings of these two clinical trials must be treated with a degree of caution. The numbers enrolled were small with 102 treated and 100 placebo in the ROXIS trial[59], and 40 treated and 20 placebo entered into the St George's trial[58]. Moreover in the St George's trial a strict comparison between treated ($n = 40$) and placebo ($n = 20$) groups was not carried out; 12 patients who were not entered (five of whom because of serious medical conditions) were added to the placebo group in the analysis. Further adequately powered trials are needed to confirm the findings of these initial investigations.

Neither of the above studies was in a position to address the fundamental problem of whether the patients enrolled had *C. pneumoniae* involvement in their arteries. The ROXIS trial randomized patients irrespective of antibody titre, and found a significant difference between treated and untreated groups, opening the possibility that roxithromycin was effective via pathways other than its antimicrobial effects. The St George's trial might have proved more instructive had all patients been randomized rather than just those with high seropositivity. If the cardioprotective effect of azithromycin had been established in the seronegative patients this could still be explained by its antimicrobial properties (as seronegative patients have been shown to have *C. pneumoniae* involvement in their arteries[18]). Again the drug could have been acting via a different pathway.

Inflammation is a key feature of both atherosclerotic plaques and (by the measurement of inflammatory markers such as CRP) of the clinical progression of atherosclerotic disease[60]. Anti-inflammatory agents such as aspirin are of recognized benefit in the prevention of reinfarction and death in patients who have suffered from myocardial infarction and occlusive vascular disease[61–67], and it has modes of action other than an antiplatelet effect alone[68]. The 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors (statins) which lower plasma cholesterol levels reduce cardiovascular mortality and morbidity rates[69,70], and lead to small but significant reductions in lesion progression[71–73]. However, it has been noted that the clinical benefit afforded by the statins was noticeable before any plaque regression occurred[74], leading to the suggestion that these agents act by reducing inflammation within the plaque, rendering it more stable[75].

In the same way the macrolide group is recognized to have anti-inflammatory properties as well as antimicrobial effects, which could reduce inflammation in the plaque leading to greater plaque stability. In Norway the mortality rate from cardiovascular disease has decreased at the same time as consumption of tetracycline antibiotics has risen[76], leading to the suggestion that this may be due to the antimicrobial action of tetracycline against *C. pneumoniae* rather than mere coincidence. However, tetracyclines are also inhibitors of the matrix metalloproteinases[77,78], which are produced by macrophages and, through destruction of the collagenous extracellular matrix in the fibrous plaque, can lead to plaque fissuring and rupture[79–81]. Again, a plausible alternative mechanism of action is available for the tetracyclines other than their antimicrobial properties. It is conceivable that the macrolides possess properties other than antimicrobial or anti-inflammatory actions to account for for the observed cardiovascular protection.

Whether antibiotics are of use in altering or slowing disease progression is not known, and trials are needed to define subsets of patients who could potentially benefit from treatment. A wider range of endpoints must be studied, to determine whether drug therapy can benefit patients with chronic vascular disease as well as offering protection against recurrent acute episodes. Given the complex interactions between cytokines and the clotting system it could be hypothesized that the protection afforded by macrolide treatment seen in the two trials is due to a decrease in the coagulability of blood and a relatively lower risk of thrombosis leading to acute vascular events. Physical evidence of plaque regression or stabilization must be sought. Patients with peripheral vascular disease represent an ideal cohort to study, given that incidence of disease is high[82,83], imaging is non-invasive, does not use radiation and is relatively cheap in the form of duplex scanning, and both acute and chronic syndromes can be examined. Widespread use of antibiotics has implications for drug resistance in the community, and further work is needed to establish the mechanism of action of these drugs to ensure they are not non-specifically reducing inflammation or acting via a non-antimicrobial pathway. If a causal relationship between atherosclerosis and *C. pneumoniae* can be established, vaccination may have great public health implications.

Conclusion

The concept of pathogens causing atherosclerosis is not new. The disease can be induced in chickens by an avian herpes virus[84,85], while attention in humans has been paid to the herpes virus group[86,87]. In common with these agents, *C. pneumoniae* cannot be shown to have a causal relationship with atherosclerosis and Koch's postulates are not fulfilled. However, even in the absence of establishing causality there is an increasing body of evidence that *C. pneumoniae* has the potential to promote a chronic immune-mediated inflammatory response that could potentially accelerate or worsen the atherosclerotic process.

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Prolonged survival in selected patients following surgical resection for pulmonary metastasis from hepatocellular carcinoma

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Background Pulmonary metastasis is the commonest site of extrahepatic spread from hepatocellular carcinoma (HCC). The aim of the present study was to evaluate the efficacy of surgical management in patients with solitary pulmonary metastases from HCC.

Methods This was a retrospective study of patients with HCC admitted for hepatectomy from July 1972 to June 1995. The records of patients who had a pulmonary resection for histologically proven pulmonary recurrence after curative hepatectomy were selected for analysis.

Results In the study interval, 380 patients with HCC underwent hepatectomy. Some 48 patients (12·6 per cent) developed pulmonary metastases documented pathologically or radiologically. Nine (seven men and two women) were suitable for curative pulmonary resection. The median disease-free survival between hepatectomy and appearance of the lung metastasis was 21 months. The median survival after pulmonary resection was 42 months, and the 1-, 2- and 5-year survival rates were 100, 78 and 67 per cent respectively.

Conclusion Pulmonary resection for metastases from HCC resulted in long-term survival in these highly selected patients.

Hepatocellular carcinoma (HCC) is common in Asia and is the second most common cancer causing death in Hong Kong[1]. With the recent advances in diagnostic modalities, perioperative management and surgical technology, more patients are suitable for hepatic resection[2]. Furthermore, the perioperative morbidity and mortality rates after hepatic resection have improved in recent years[3,4]. The long-term outcome of patients with HCC remains poor because of a high incidence of recurrence after hepatic resection.

Although intrahepatic recurrence predominates, pulmonary metastasis is the commonest site of extrahepatic spread[5]. The role of surgery for a solitary pulmonary metastasis is not known. The aim of the present study was to evaluate the efficacy of surgery in treating patients with a solitary pulmonary metastasis after curative hepatic resection.

Patients and methods

Between July 1972 and June 1995, 380 patients with HCC underwent hepatic resection. The preoperative investigations, operative technique and postoperative management have been documented elsewhere[3,4]. All patients were followed up regularly at intervals of 1–3 months with physical examination, chest radiography and liver biochemistry tests. Since 1984 follow-up has included regular measurement of serum α-fetoprotein concentration and percutaneous ultrasonography of the liver remnant. Computed tomography of the lung was done if the chest radiograph was abnormal.

Patients with a solitary pulmonary metastasis and no concomitant intrahepatic recurrence were selected for surgery. After resection of the pulmonary recurrence, patients received adjuvant chemotherapy (six doses of intravenous epirubicin 60 mg/m^2) and careful life-long follow-up. Further pulmonary resection was performed for patients with reappearance of another solitary metastasis if there was no liver recurrence. Patients with uncontrolled liver disease or multiple pulmonary metastases were offered chemotherapy.

Both disease-free survival and overall survival were measured from the date of hepatic resection. The survival rates were calculated according to Kaplan and Meier[6].

Results

Among the 380 patients who had hepatectomy for HCC, 48 (12·6 per cent) developed pulmonary metastases documented radiologically or pathologically. Nine patients, seven men and two women, were suitable for curative pulmonary resection because their hepatic disease was cleared or well controlled.

The clinical parameters of these nine patients are summarized in *Table 1*. The median disease-free interval between hepatectomy and appearance of the lung metastasis was 21 months. There was no operative or hospital death among the nine patients who had pulmonary resection. Two patients (6 and 9) developed hepatic recurrence before the discovery of pulmonary metastases, but the hepatic recurrence was treated successfully by transarterial oily chemoembolization (TOCE) and intralesional alcohol injection respectively. Three patients (2, 3 and 5) developed recurrent disease in the liver after the pulmonary resection. Two patients (3 and 6) each developed a second pulmonary metastasis and required repeat thoracotomy for resection at 12 and 13 months after the first lung resection.

The median duration of follow-up after hepatectomy was 53 months. The median survival after pulmonary resection was 42 months. The 1-, 2- and 5-year survival rates after hepatectomy were 100, 78 and 67 per cent respectively. Five patients were still alive and four of them had no evidence of recurrent disease. One patient (no. 9)

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Table 1 Clinical details of patients who had pulmonary resection for metastases from hepatocellular carcinoma

Patient no.	Sex	Age (years)	Hepatic lobectomy	Related liver disease	Disease-free survival (months)	Pulmonary resection	Survival (months)	Outcome
1	M	68	Right	n.a.	20	R lower lobectomy	22	Dead, free from disease
2	M	62	Left	n.a.	51	Wedge excision	93	Dead with disease in liver
3	M	25	Right extended	HBsAg$^+$	10	Wedge excision and right lower lobectomy	34	Dead with disease in liver
4	F	33	Right	n.a.	11	Wedge excision	15	Dead, free from disease
5	M	58	Right	HBsAg$^+$, cirrhosis	11	Wedge excision	80	Alive with disease in liver
6	M	38	Right extended	HBsAg$^+$, CAH	21	Wedge excisions	53	Alive with no evidence of disease
7	M	45	Right	HBsAg$^+$, CAH	23	Wedge excision	81	Alive with no evidence of disease
8	M	60	Right	Cirrhosis	23	R lower lobectomy	74	Alive with no evidence of disease
9	F	50	Left extended	HBsAg$^+$, cirrhosis	26	L lower lobectomy	127	Alive with no evidence of disease

HBsAg$^+$, hepatitis B antigen positive; CAH, chronic active cirrhosis; n.a. not available

is alive more than 8 years after pulmonary resection (more than 10 years after hepatectomy) and remains disease free.

Thirty-nine patients developed pulmonary metastases but were not suitable for resection because of the presence of uncontrolled liver disease or multiple pulmonary metastases. Twenty of them accepted systemic chemotherapy. Twenty-three of the 39 patients had documented hepatic recurrence in addition to the pulmonary metastases. The median disease-free interval before the appearance of lung metastases was 8 months. The median survival after diagnosis of the pulmonary metastases was 14 months, and the 1-, 2- and 5-year survival rates after hepatectomy were 42, 32 and 10 per cent respectively.

Discussion

The postoperative morbidity and mortality rates of patients who have hepatectomy for HCC have been improving in recent years[3,4]. After successful resection, the recurrence rate is disappointingly high; as many as 80–85 per cent of patients succumb to recurrent disease within the first 18 months of hepatectomy[7].

Although the lung is the commonest site for extrahepatic spread from HCC, only a few case reports exist in the English literature describing the management of this condition[8,9]. Therefore, the treatment strategy and prognosis of patients with pulmonary metastases from HCC are largely unknown.

Some investigators consider any extrahepatic recurrence of HCC to be a contraindication for further treatment[10]. Indeed, the result of treatment for extrahepatic recurrent HCC is poor. In a study of 34 patients with extrahepatic metastases (21 pulmonary) treated with chemotherapy, the median survival and 1-year survival rate were 4·6 months and 20 per cent respectively[11]. The effect of chemotherapy on pulmonary metastases is difficult to predict. Some of the present patients had a good response to systemic chemotherapy and a prospective study is underway to document the result.

The authors have reported previously that surgical resection is effective in selected patients with an isolated extrahepatic recurrence of HCC and offers the only chance of long-term survival[12]. Therefore, with this rationale, patients with a solitary pulmonary metastasis were managed actively.

Most pulmonary metastases of HCC are multiple[13] and are not amenable to surgical resection. Solitary pulmonary metastases may be encountered occasionally. If considered resectable, the patient should be investigated to exclude the presence of other metastasis, especially in the liver remnant, before embarking on surgery. However, if the hepatic recurrence can be cleared by re-resection or controlled by local ablation using intralesional alcohol injection or TOCE, pulmonary resection for solitary metastasis may still be considered.

Even when a metastasis seems solitary, it is generally assumed that occult metastases are present. Therefore, systemic chemotherapy was given to all patients after resection of the pulmonary metastasis. The patients who had surgical resection for a curable pulmonary metastasis had a survival rate comparable to that of patients without recurrence after hepatectomy. However, this was a highly selected group of patients as the pulmonary metastases appeared late, a median of 21 months after hepatectomy, in contrast to 8 months in the patients with irresectable disease.

Although the number of patients suitable for resection of a pulmonary metastasis after curative hepatectomy for HCC is small, some long-term survivors will benefit. An active approach to the management of resectable pulmonary metastases from HCC is justified in selected patients.

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Effect of lithium γ-linolenate on the growth of experimental human pancreatic carcinoma

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Background The lithium salt of γ-linolenic acid (Li-GLA) is growth inhibitory to pancreatic cancer cells *in vitro* and is reported to prolong the survival of patients with pancreatic cancer. The effect of Li-GLA on the growth of human pancreatic carcinoma *in vivo* is not known. In this study the effect of parenterally administered Li-GLA on the growth of human pancreatic carcinoma in nude mice was tested.

Methods Pancreatic tumours were produced in nude mice by subcutaneous implantation of MIA PaCa-2 cells. This cell line is sensitive to Li-GLA *in vitro*. Mice were randomly treated with intraperitoneal, intravenous or intratumoral Li-GLA. Each group also had controls.

Results Both intravenous and intraperitoneal administration of Li-GLA had no significant effect on tumour growth or tumour phospholipid fatty acid composition. Intratumoral administration of Li-GLA was, however, associated with a significant antitumour effect.

Conclusion Within the limitations of this tumour model, the benefit seen with intravenous Li-GLA in patients with pancreatic carcinoma cannot be explained by tumour growth inhibition. Local administration appears to be more effective than intravenous or intraperitoneal therapy.

Adenocarcinoma of the pancreas is a common cause of death worldwide and appears to have the worst prognosis of all common human cancers[1]. Most patients present with advanced, irresectable disease and there is no effective chemotherapy. Prolongation of survival, if any, is modest and is achieved at the expense of side-effects that impair the quality of life.

Essential fatty acids, such as γ-linolenic (GLA) and eicosapentaenoic (EPA) acids, appear to have many beneficial effects in cancer. In addition to a direct growth inhibitory effect, thought to be mediated by increased lipid peroxidation, they have an antimetastatic effect[2,3], a beneficial effect on the cachexia that accompanies cancers such as pancreatic cancer[4], and may potentiate the effect of other anticancer agents[5,6]. GLA and EPA have no serious side-effects so quality of life is not impaired by treatment.

The lithium salt of GLA (Li-GLA) is a water-soluble, injectable, and relatively pure and stable preparation of this fatty acid. Li-GLA has a dose- and time-dependent selective growth inhibitory effect on human pancreatic cancer cell lines *in vitro*[7]. Treatment with Li-GLA also prolonged the survival of patients with irresectable pancreatic cancer in a dose-dependent fashion in a phase II study[8]. However, the effect of Li-GLA on the growth of human pancreatic carcinoma *in vivo* is not known. The aim of this study was to determine the effect of parenterally administered Li-GLA on the growth of human pancreatic carcinoma using an *in vivo* model of tumour growth.

Materials and methods

BALB/c nude mice (Harlan, Bicester, UK) aged 6–8 weeks were housed in groups of four to six animals in polycarbonate cages fitted with filter lids and sterilized woodchip bedding in a dedicated pathogen-free clean isolation unit with controlled temperature (19–21°C) and humidity (greater than 50 per cent) with 12-h light–dark cycles. Throughout the experiment they were allowed free access to sterilized standard mouse diet (rat and mouse breeding diet No. 3; Special Diet Services, Essex, UK) with water *ad libitum*. All experiments were conducted in conformity with the laws and regulations controlling experiments on live animals by the Home Office.

Tumour transplantation and measurement

Human pancreatic tumours were produced subcutaneously on the left flank in mice by subcutaneous inoculation of 10^5 MIA PaCa-2 cells (for intraperitoneal Li-GLA experimentation) or by transplanting a small fragment of a tumour produced by MIA PaCa-2 inoculation in another Balb/c mouse (all other experiments). Irrespective of the method of inoculation, the resulting tumours behaved in a similar fashion, characterized by a progressive increase in tumour volume without local invasion, distant metastasis or any significant loss of host body-weight. Tumour volume was calculated from calliper measurements of the greatest transverse (width) and longitudinal (length) diameters using the formula[9]: $\text{volume} = \text{length} \times \text{width}^2/2$. When two subsequent tumour volume measurements at weekly intervals showed progressive growth, the mice were divided randomly into treatment and control groups.

Treatment

Intraperitoneal lithium γ-linolenate. Li-GLA was supplied as a solution containing 140 mg Li-GLA per ml in 12·75 per cent ethanol. The treatment group received Li-GLA at a total dose of 0·5 mg/g ($n = 7$) or 1 mg/g body-weight (maximum tolerated dose in preliminary experiments) ($n = 11$), given in ten daily intraperitoneal injections dissolved in normal saline. The control groups received a similar dose of lithium salt of oleic acid in

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12·75 per cent ethanol dissolved in normal saline ($n = 5$ and $n = 8$ respectively).

Intravenous galactosomal lithium γ-linolenate. The galactosomal preparation contained Li-GLA 1·5 per cent w/v and galactolipids from oats, 10 per cent in water at pH 7·5. The galactosomes were filtered through a 45-μm filter. Particle size measurements indicated a bimodal distribution with peaks of particle sizes of approximately 70 and 150 nm respectively; the particle size cut-off limit was 300 nm (data supplied by manufacturer). The treatment group ($n = 17$) received undiluted galactosomal Li-GLA at a total dose of 1 mg/g body-weight (maximum tolerated dose) in ten daily tail-vein bolus injections (0·1 mg/g daily). The control group ($n = 17$) received an equal volume of blank galactosomes of the same galactolipid composition but without Li-GLA.

Intratumoral lithium γ-linolenate. The treatment group ($n = 9$) received Li-GLA (140 mg/ml in 12·75 per cent ethanol) and the control group ($n = 7$) received lithium oleate (140 mg/ml in 12·75 per cent ethanol). The volume injected was dependent on tumour volume. Tumours up to the volume of 500 mm^3 received 100 μl, tumours of 501–1000 mm^3 received 200 μl and those over 1000 mm^3 received 300 μl. In preliminary experiments these volumes were administered safely and easily for the given tumour volume. Approximately half the volume of the fatty acid was administered in the centre of the tumour and the rest subcutaneously around the tumour.

Tumour response

Tumour response was assessed from the relative change in tumour volume compared with the volume at the beginning of therapy. The volume was measured at the beginning and end of treatment, and then weekly for 4 weeks. For the intratumoral injection groups, tumour volume was measured just before the injection and then weekly for 4 weeks.

Adverse effects

The mice were inspected daily during the experiment for any signs of disease, distress or haematuria. Their weight was also measured at the beginning and end of the treatment, and then weekly for 4 weeks.

Fatty acid analysis of tumours

This was performed at the end of follow-up. In each experiment, animals from treatment and control groups were killed by cervical dislocation and tumours were quickly removed. Tumour tissue was snap frozen in liquid nitrogen after discarding the central necrotic portion of the tumour and stored at − 80°C. Samples were shipped in dry ice to Efamol Research Laboratories (Kentville, Nova Scotia, Canada), where the analysis was performed blind. The methodology has been published[10]. In summary, total lipids were extracted from the tumours with chloroform–methanol[11], the phospholipid fraction was separated by thin-layer chromatography, and fatty acids of the total lipid and phospholipid fractions were methylated and analysed by reverse-phase high-performance liquid chromatography. The amount of each fatty acid is presented as the percentage of total fatty acids.

Statistical analysis

The difference in tumour volume and body-weight between animals in treatment and control groups was studied with the Mann–Whitney *U* test. The fatty acid composition of the tumours was compared with the *t* test for two independent samples. $P < 0.05$ was considered significant.

Results

The tumour volumes and mouse body-weights were not statistically different between treatment and control groups at the beginning of treatment in any of the experiments.

Intraperitoneal γ-linolenate

Tolerance and adverse effects. No significant adverse effect or deaths were noted in the group treated intraperitoneally with Li-GLA 0·5 mg/g. One animal in the control group died from an unknown cause. A dose of 1 mg/g was toxic, and was associated in five animals in the treatment group with the development of chemical peritonitis and death. Post-mortem examination revealed intraperitoneal adhesions. No adverse effects or deaths were seen in the control group. No significant difference in body-weight was seen between the treatment and control groups at both doses, but Li-GLA 1 mg/g was associated with some loss of weight at the end of the treatment interval.

Effect on tumour growth. Intraperitoneal Li-GLA therapy, at both 0·5 mg/g (data not shown) and 1 mg/g doses (*Fig. 1*), had no significant effect on tumour volume compared with controls.

Intravenous γ-linolenate

Tolerance and adverse effects. Galactosomal Li-GLA (and control galactosomes) was well tolerated with no adverse effects. No significant difference in body-weight was seen between treatment and control groups.

Effect on tumour growth. No significant difference in tumour volume was seen between the treatment and control groups (*Fig. 2*).

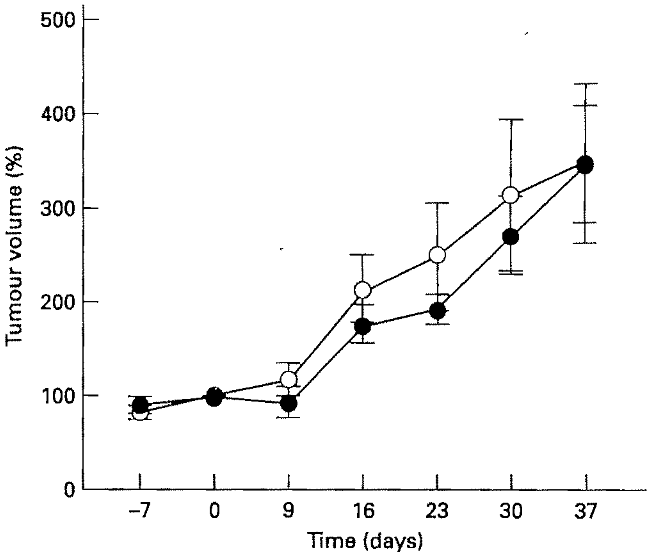

Fig. 1 Tumour volume of mice treated intraperitoneally with the lithium salt of γ-linolenic acid (●; $n = 11$) or of oleic acid (○; control, $n = 8$) at a dose of 1·0 mg/g, presented as a percentage of the tumour volume at the beginning of therapy. The treatment interval was from day 0 to day 9. Values are mean(s.e.m.)

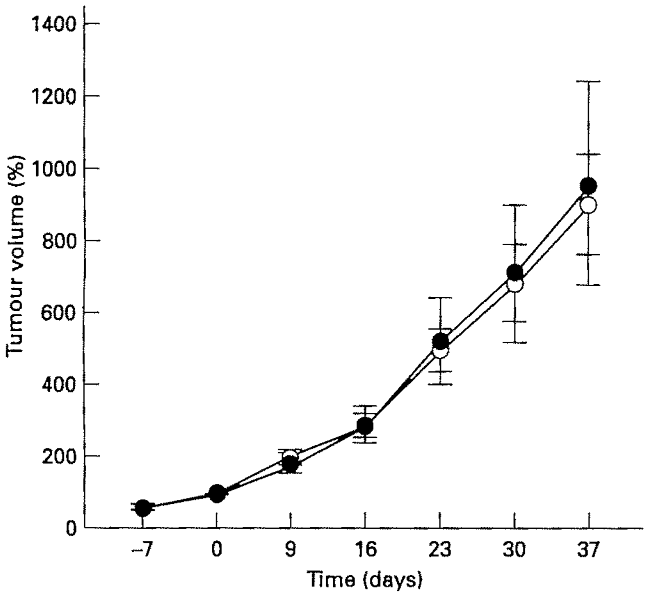

Fig. 2 Tumour volume of mice treated intravenously with galactosomal lithium salt of γ-linolenic acid 1·0 mg/g (●; $n = 17$) or blank galactosomes (○; control, $n = 17$), presented as a percentage of the tumour volume at the beginning of therapy. The treatment interval was from day 0 to day 9. Values are mean(s.e.m.)

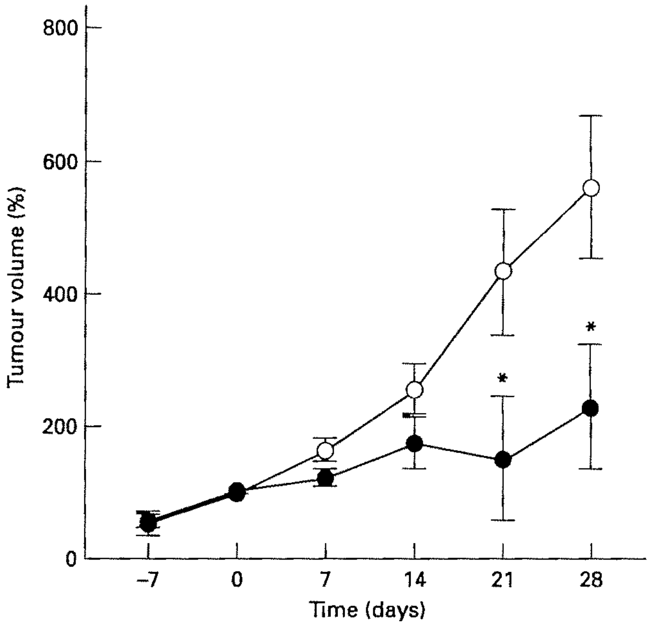

Fig. 3 Tumour volume of mice treated intratumorally with the lithium salt of γ-linolenic acid (●; $n = 9$) or of oleic acid (○; control, $n = 7$), presented as a percentage of the tumour volume at the time of injection (time = 0). Values are mean(s.e.m.). *$P = 0{\cdot}03$ *versus* control, Mann–Whitney *U* test

Table 1 Effect of therapy on the essential fatty acid composition of tumour phospholipids

	Intravenous therapy		Intraperitoneal therapy		Intratumoral therapy	
Fatty acid	Li-GLA	Control	Li-GLA	Control	Li-GLA	Control
Oleic acid	12·46(0·81)	13·42(0·31)	12·90(0·40)	12·96(0·85)	10·76(0·67)	13·39(1·37)
Linoleic acid	11·43(0·05)	11·34(0·14)	13·00(0·76)	13·20(0·60)	13·10(0·38)	12·90(1·73)
GLA	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
DGLA	1·18(0·03)	1·08(0·04)	1·40(0·17)	1·40(0·08)	1·23(0·04)	1·41(0·10)
AA	13·79(0·55)	13·09(0·64)	13·10(0·28)	13·60(0·52)	15·87(0·63)	14·20(0·35)
Adrenic acid	2·27(0·32)	1·95(0·21)	1·30(0·10)	1·35(0·30)	1·77(0·06)	1·89(0·40)
EPA	n.d.	n.d.	0·30(0·03)	0·35(0·07)	n.d.	n.d.
DPA	1·75(0·10)	1·67(0·08)	1·47(0·09)	1·39(0·15)	1·52(0·17)	1·66(0·16)
DHA	7·65(0·10)	7·48(0·20)	7·00(0·22)	5·73(1·17)	6·62(0·26)	6·57(0·83)

Control animals received lithium oleate (intraperitoneal and intratumoral groups) or blank galactosomes (intravenous group). Values are mean(s.e.m.) percentages of total fatty acids from three to five tumours. Li-GLA, lithium salt of γ-linolenic acid; DGLA, dihomo-γ-linolenic acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid ($n = 3$); DHA, docosahexaenoic acid. n.d., Not detected

Intratumoral γ-linolenate

Tolerance and adverse effects. Li-GLA injection was associated with patchy necrosis of skin overlying the tumour in three animals but this healed with no consequences. No adverse effects were noted in the control group. No significant difference in body-weight was seen between the treatment and control groups.

Effect on tumour growth. A statistically significant reduction ($P = 0{\cdot}03$) in tumour volume was seen in the treatment group 3 and 4 weeks after the injection (*Fig. 3*). Two tumours in the treatment group regressed completely following the injection and failed to reappear during a 4-week follow-up. No tumour regression was seen in the control group.

Fatty acid analysis of tumours

There was no significant difference, compared with control groups, in the tumour phospholipid fatty acid composition at the end of the follow-up period in any of the experiments (*Table 1*). In particular there was no increase in *n*-6 fatty acids (GLA or its elongation products). Similar results were seen with tumour total lipid analysis (data not shown).

Discussion

Although Li-GLA is growth inhibitory to pancreatic cancer cell lines *in vitro*[7] and in an open phase II clinical study prolonged the survival of patients with pancreatic cancer in a dose-dependent fashion[8], it is still not known whether Li-GLA can inhibit tumour growth *in vivo*. Assessment of tumour response in patients with pancreatic carcinoma by radiological means is far from satisfactory. An animal model of subcutaneous human pancreatic cancer provides a good opportunity to study the tumour response to Li-GLA.

This study differs from many previous fatty acid studies in animal tumour models in the form of fatty acid used (lithium salt), in the route of administration (parenteral as opposed to oral) and in that the treatment was begun only when the tumours were established and growing, rather than at the time of implantation or before, thus closely mimicking the clinical situation. The results show that Li-GLA, at the doses administered, had no significant effect on tumour growth with intravenous or intraperitoneal administration. This was despite the fact that the MIA PaCa-2 cell line was sensitive to Li-GLA *in vitro* at low micromolar concentrations[7], and that the dose administered (on a body-weight basis) and the regimen used was similar to the one used in the phase II clinical study[8] where Li-GLA appeared to prolong survival. The differences in the protocols are that the intravenous Li-GLA was administered in galactosomal form (as opposed to free Li-GLA) as a bolus, rather than by continuous infusion, and that no oral GLA was given following the completion of parenteral therapy. It would seem unlikely that these factors could have influenced the results. Galactosomal Li-GLA was used as it allowed a higher dose of Li-GLA to be administered as a bolus compared with the free form and without the side-effects, such as haemoglobinuria and thrombophlebitis, associated with free Li-GLA[8]. Oral GLA has proved ineffective as an antitumour agent, albeit in smaller doses and in the form of evening primrose oil, in previous controlled clinical studies involving colorectal and hepatocellular carcinoma[12,13]. In the two studies of fatty acid therapy of irresectable pancreatic carcinoma reported to date, no tumour response was seen among evaluable patients with oral fish oil therapy[4] and no attempt was made to assess the tumour response in the phase II study using Li-GLA[8].

The lack of effect on tumour growth *in vivo* with intravenous and intraperitoneal Li-GLA may be explained by several mechanisms. Albumin binding[7] and antioxidants may interfere with the growth inhibitory effect of Li-GLA. However, the most important reason appears to be that insufficient fatty acid reached the tumour to influence tumour growth, as shown by fatty acid analysis of tumours. A relatively poor tumour GLA uptake was also confirmed by the present authors in studies using radiolabelled Li-GLA (data not shown), and by others[14]. Fatty acid analysis revealed that there was no significant increase in GLA or its derivatives in tumour phospholipids even in tumours removed at the end of treatment, except in the intratumoral Li-GLA group where an increase in GLA was found 24 h after the injection (data not shown). Subcutaneous tumours in mice usually have a poor blood supply, which may be contributory to this low uptake, but pancreatic cancer is a poorly vascularized tumour in humans. This is at least partially responsible for the failure of other anticancer agents in this disease as it may be difficult to achieve a satisfactory level of chemotherapeutic drug in the tumour using conventional methods of administration. The success of intratumoral therapy, however, confirms that, if an adequate dose of fatty acid is delivered to the tumour, an antitumour effect can be achieved *in vivo*[15]. Until further improvements are achieved in fatty acid delivery mechanisms that would ensure a high fatty acid uptake by the tumour, this may be feasible only by locoregional administration. Locoregional chemotherapy such as intra-arterial or intratumoral therapy is feasible and effective in pancreatic carcinoma[16–18]. This study suggests that Li-GLA may be useful in this context.

The present study suggests that the prolongation of survival seen in the phase II study may not be explained by tumour growth inhibition. Essential fatty acids such as GLA and EPA have other benefits in cancer such as antimetastatic and anticachectic effects[2–4]. In the tumour model used here, distant metastasis and significant weight loss were not seen; thus it was not possible to study the effect of GLA on these aspects of tumour behaviour. Achieving tumour growth inhibition with fatty acids *in vivo* may be more likely with a locoregional approach than with conventional means.

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tumour that grew into the bile duct. Tumour stage was also defined according to the classification of the Liver Cancer Study Group of Japan[6].

Surgical specimens were fixed in 10 per cent formalin and processed for light microscopy. Paraffin-embedded blocks were sectioned and the sections were stained with haematoxylin and eosin. The following pathological factors were examined: invasion into the portal vein; perineural invasion or invasion of lymphatic vessels; intrahepatic metastasis; and infiltration of the resected surface of the liver or the surface of the biliary duct by cancer cells. Infiltration of resection margins was defined as the presence of cancer cells within 5 mm of the resected surface.

To exclude HCC and mixed HCC and cholangiocarcinoma, histochemical and immunohistochemical analysis was also undertaken. Immunohistochemical studies were performed by the avidin–biotin complex method. The antibodies used were mouse monoclonal antibodies against cytokeratin (CK) 7 (diluted 1:50; DAKO, Carpinteria, California, USA), CK 8 (diluted 1:50; DAKO) and CK 19 (diluted 1:50; DAKO). Samples were also stained with mucicarmine and alcian blue for detection of mucin in the neoplastic cells.

Histological and histochemical criteria for identification of ICC were as described by Maeda *et al.*[7]: 1, small glandular structure composed of small cuboidal cells with round nuclei and abundant fibrous stroma; and 2, focal or predominant immunostaining specific for CK 19.

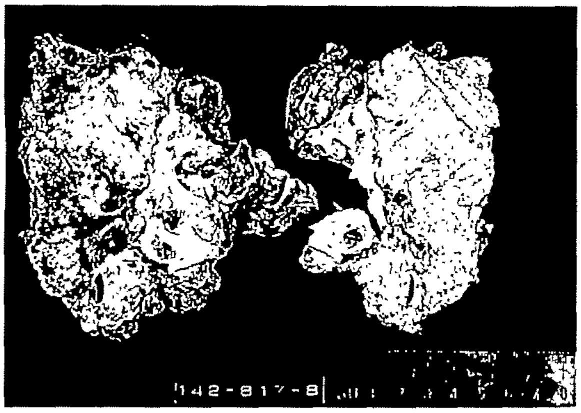

Fig. 2 Intrahepatic cholangiocarcinoma of the periductal infiltrating type. A non-nodular tumour is observed as fibrous thickening of Glisson's sheath

Results

The clinical background and outcome of the patients who had resection of ICC, and the histological nature of the tumours, are summarized in *Table 1*. The mean diameter of the tumour was 77 (range 22–130) mm. Four tumours were classified as stage II, two as stage III, five as stage IV-A and one as stage IV-B. The tumour at stage IV-B had invaded and/or metastasized into the peritoneal cavity. Preoperative serum levels of carcinoembryonic antigen were raised in three patients with tumours at stages IV-A and IV-B. The serum level of α-fetoprotein was raised in only one patient (no. 6).

Nine tumours were classified as mass-forming type and three as periductal infiltrating type. Two cases of the periductal infiltrating type (patients 2 and 3) were accompanied by hepatolithiasis and three of the mass-forming type (patients 6, 10 and 12) were accompanied by chronic active hepatitis related to infection by hepatitis C virus. All patients underwent lobectomy or extended lobectomy with or without resection of the extrahepatic bile ducts. Three patients were left with metastatic nodules in the remnant liver (patients 8 and 10) or the peritoneal cavity (patient 12) after operation. Four patients with stage II disease remained alive without disease after 27–84 months. Two patients (nos 3 and 9) died from liver failure within a few months after operation and the remaining six patients died from the disease (patient 6) or remained alive with disease after 2–30 months (patients 7, 8, 10, 11 and 12).

In terms of morphology, squamous metaplasia was focally admixed with adenocarcinoma in the tumour in patient 3. All tumours of the periductal infiltrating type had a small glandular structure with production of mucin and abundant fibrous stroma. More than half of the tumours of the mass-forming type formed indistinct

Table 1 Details of patients with intrahepatic cholangiocarcinoma

Patient no.	Age (years)	Sex	Diameter (mm)	Stage	Histological type	vp	im	pn or ly	Operative procedure	tw	b-tw	Outcome
Periductal infiltrating type												
1	49	M	22	II	tub2	−	−	+	LL + EHB	−	−	AOD (27 months)
2	72	F	60	II	tub1	−	−	+	LL + EHB	−	−	AOD (34 months)
3	64	F	70	III	tub2*	−	+	+	LL	+	+	DOF (2 months)
Mass-forming type												
4	58	M	30	II	poor	+	−	−	LL	−	−	AOD (34 months)
5	57	M	37	II	poor	−	−	−	RL	+	−	AOD (84 months)
6	60	M	130	III	tub2	+	+	−	RL	+	−	DOD (27 months)
7	63	M	79	IV-A	poor	+	+	+	exRL	+	+	AWD (5 months)
8	78	M	80	IV-A	poor	+	−	+	LL	+	−	AWD (30 months)
9	63	F	102	IV-A	poor	+	+	+	RL	+	+	DOF (3 months)
10	69	F	130	IV-A	tub2	+	+	+	LL	+	+	AWD (2 months)
11	55	M	125	IV-A	tub2	+	+	+	exRL	+	−	AWD (5 months)
12	75	F	60	IV-B	tub2	+	+	+	LL	+	−	AWD (4 months)

tub1, Well differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma; poor, poorly differentiated tubular adenocarcinoma; *squamous metaplasia focally admixed in tub2; vp, invasion into the portal vein; im, intrahepatic metastasis; pn, perineural invasion; ly, invasion of lymphatic vessel; LL, left lobectomy; RL, right lobectomy; EHB, resection of the extrahepatic bile duct; exRL, extended right lobectomy; tw, infiltration of the resected surface of the liver; b-tw, infiltration of the resected surface of the biliary duct; AOD, alive without disease; DOF, dead as a result of postoperative liver failure; AWD, alive with disease; DOD, dead as a result of disease

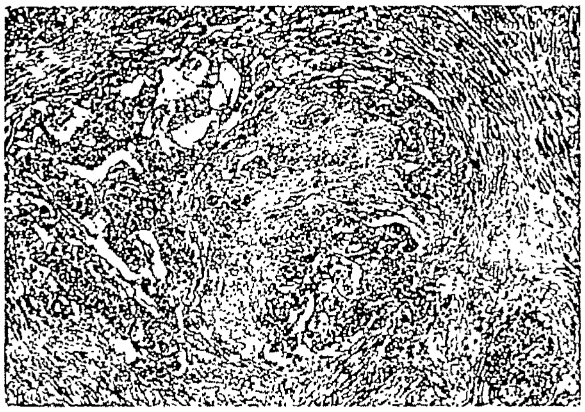

Fig. 3 Perineural or neural invasion by a periductal infiltrating type of tumour (patient 1). (Haematoxylin and eosin stain, original magnification × 100)

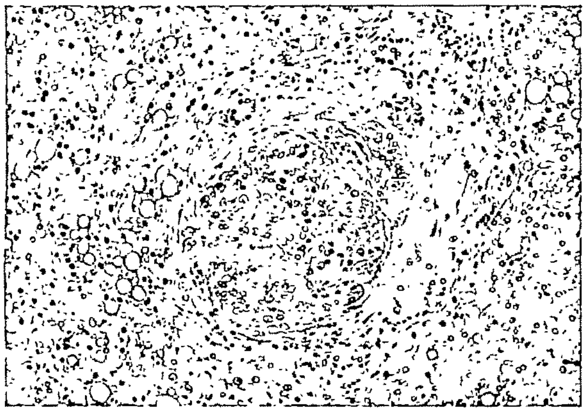

Fig. 4 Invasion of the peripheral portal vein by a tumour of the mass-forming type (patient 10). Haematoxylin and eosin stain, original magnification × 200)

glandular structures and had scant fibrous stroma. No production of mucin was detected in three tumours in patients 7, 8 and 9. Immunohistochemically, neoplastic cells of all but one tumour reacted positively with antibodies against CK 7 and CK 19, and one tumour of the mass-forming type reacted only with antibody against CK 19.

Portal vein invasion, intrahepatic metastases and perineural or lymphatic invasion were present in zero, one and all three of periductal infiltrating type tumours, and in eight, six and six of nine mass-forming type tumours respectively (*Figs 3* and *4*). Tumours of the periductal infiltrating type were at a relatively early stage compared with those of the mass-forming type.

Although all patients underwent lobectomy or extended lobectomy, four had positive bile duct margins with perineural or lymphatic invasion in Glisson's sheath. No histological evaluation for nodal metastasis was performed in the present study because regional lymph nodes were not swollen and were dissected out in only four patients at operation.

Discussion

The mode of spread of ICC has been studied. Nakajima *et al.*[8] reported that the portal venous system is the main route of intrahepatic metastasis and, moreover, that ICC extends along the nerves from the hilum to the extrahepatic area. They concluded that histological differentiation contributed to the mode of spread of the tumour, although they did not mention any relationship with gross appearance. Ohashi *et al.*[5] reported that the incidence of vascular and perineural invasion was higher in cases of tumours of the spicular-forming type than in tumours of other macroscopic types (mass-forming and periductal extension types). Yamamoto and co-workers[4] demonstrated that vascular involvement in tumours of the mass-forming type led to intrahepatic metastasis and decreased long-term survival, whereas tumours of the infiltrating type spread along Glisson's capsule, resembling carcinomas of the extrahepatic bile duct. Yamanaka *et al.*[9] demonstrated that ICC of the mass-forming type without biliary stricture behaves more like HCC, whereas ICC

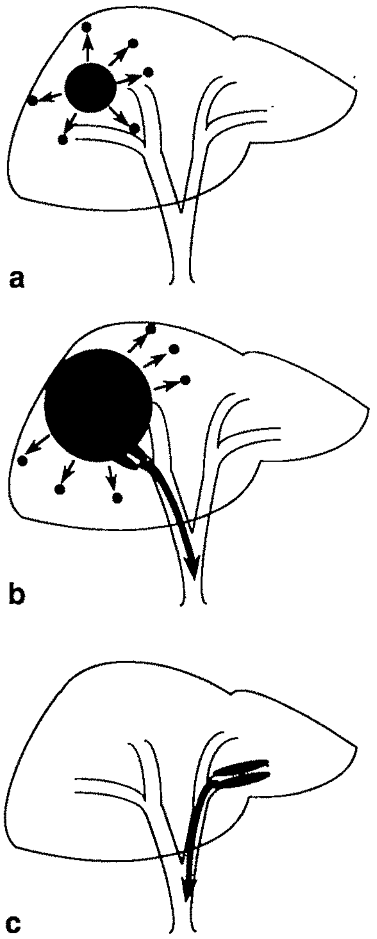

Fig. 5 Mode of spread of intrahepatic cholangiocarcinoma according to the classification by gross appearance. a The mass-forming type at the early stage. The neoplastic cells spread to the liver via the portal system (→). b The mass-forming type at a late stage. The tumour invades Glisson's sheath and spreads via both the portal and the lymphatic system. c The periductal infiltrating type. The neoplastic cells spread via the lymphatic system into Glisson's sheath (→). •, Intrahepatic metastasis

with biliary stricture is more like hilar or extrahepatic bile duct carcinoma. In this study, the mode of spread of ICC was considered (*Fig. 5*). At relatively early stages, a tumour of the mass-forming type spreads into the liver via the portal vein system, with formation of intrahepatic metastatic nodules, as does HCC[10]. As it becomes larger, the tumour starts to involve Glisson's sheath and to invade Glisson's sheath through lymphatic vessels. By contrast, ICC of the periductal infiltrating type spreads along Glisson's sheath via lymphatic vessels, with a low incidence of spreading via the portal system.

The histogenesis of ICC has been investigated by several groups. Sell and Dunsford[11] investigated the histogenesis of HCC and ICC in rats, and postulated that both HCC and ICC arise from pluripotent liver stem cells. D'Errico *et al.*[12] demonstrated that HCC and peripheral cholangiocellular carcinoma might share a common histogenesis by immunohistochemical staining for cytokeratins and detection of messenger RNA for albumin. In the present study, most tumours of the periductal infiltrating type were well differentiated, whereas more than half of the tumours of the mass-forming type were poorly differentiated and morphologically similar to HCC. Moreover, portal vein invasion and intrahepatic metastasis were frequently associated with the mass-forming type of ICC but not with the periductal infiltrating type. These findings support the hypotheses proposed by the authors cited above. The results of the present study suggest that the mass-forming type of ICC might behave biologically in a similar manner to HCC.

The surgical management of ICC has been described by several groups. Yamamoto *et al.*[4] suggested that anatomic and extensive hepatectomy is the rational procedure for mass-forming ICC and that hepatectomy with extrahepatic duct excision and hilar lymph nodal resection is the rational procedure for infiltrating ICC. Ohashi *et al.*[5] suggested that, with the goal of a permanent cure, liver resection with tumour-free margins should be performed in cases of the mass-forming type. By contrast, for tumours of the periductal extension and spicular-forming types, aggressive treatment, namely a combination of extensive liver resection, lymph node dissection and effective adjuvant anticancer therapy, should be provided. The present results support these proposals. Hepatectomy with resection of the extrahepatic bile duct and hilar lymph nodes should be considered for ICC of the mass-forming type with invasion of Glisson's sheath and for the periductal infiltrating type of ICC.

Acknowledgements

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Short note

Preliminary experience with percutaneous cryotherapy of liver tumours

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Surgical resection is the therapy of choice for hepatic malignancy and yet only 30 per cent of patients with primary hepatic lesions and 10–20 per cent of those with liver metastases are potential candidates[1]. Since 1994, the authors have offered patients with irresectable liver tumours open cryosurgery using high-performance cryoprobes as an alternative treatment.

The aim of this investigation was to evaluate whether percutaneous hepatic cryotherapy (PHCT) may be considered as an alternative to open hepatic cryosurgery in a selected group of patients

Patients and methods

Between August 1995 and November 1997, eight patients with irresectable liver malignancy were selected for PHCT because of contraindications to open cryosurgery or refusal of the open procedure (*Table 1*). Only patients with liver tumours that could be visualized clearly by ultrasonography were included. For optimal ultrasonographic imaging and application of the cryoprobes (Cryo 6; ERBE, Tübingen, Germany) two patients required a complete left-lateral position and three needed a half left-side position. Under general anaesthesia thin cannulas were placed with ultrasonographic guidance to locate dilators over corresponding guidewires. For tumours with diameters smaller than 2 cm one cryoprobe was placed in the centre of the lesion. For tumours 2–5 cm in diameter it was essential to use at least three probes with simultaneous freezing to achieve complete tumour destruction[2]. Freezing was monitored by ultrasonography and had to exceed the tumour margin by at least 1 cm. Successful tumour destruction was determined by magnetic resonance imaging (MRI) 1 week and then every 3 months after cryotherapy.

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Results

Ultrasonographically guided percutaneous cryoablation was successful in all patients without the need to convert to open operation. There were no intraoperative or postoperative complications. All patients recovered quickly, as expressed by a mean(s.d.) hospital stay of 6(3) days.

The first MRI study showed complete destruction of all metastases smaller than 4·5 cm ($n = 5$) with no local recurrence within a follow-up interval of 5–27 months.

Three metastases with a diameter of more than 4·5 cm were either only 95 per cent destroyed ($n = 2$) or recurred locally after 3 months ($n = 1$) (*Table 1*).

One of two patients with hepatocellular carcinoma showed complete destruction of a 7-cm tumour at the first MRI study and a small paracaval recurrence 12 months after PHCT, which was treated by additional chemoembolization. The second patient with hepatocellular carcinoma with a tumour greater than 10 cm in diameter remaining after initial chemoembolization had primary destruction of 80 per cent for 1 month (*Table 1*).

Discussion

In patients with irresectable liver metastases percutaneous alcohol injection and laser-induced thermotherapy is accepted as an alternative and effective treatment compared with the corresponding open procedures[3,4]. How-

Table 1 Percutaneous cryotherapy – patients, tumour characteristics, cryoprobes and recurrences

Patient no.	Sex	Age (years)	Tumour size (cm)	Tumour localization (liver segment)	No. of hepatic surgical pretreatments	No. of cryoprobes	Primary destruction (%)	Local recurrence (months)	Hepatic recurrence (months)	Follow-up after cryotherapy (months)
Liver metastases										
1	F	69	4·0	VIII	1	3	100	—	10	27
2	F	63	3·0	VII	1	3	100	—	4	12
3	F	30	6·0	IV–VIII	2	4	95	1	—	8
4	M	64	2·0	IV	1	2	100	—	—	
			5·0	VIII		4	95	1		8
5	M	58	3·5	VII	1	3	100	—	—	5
6	F	34	2·0	V	—	2	100	—	—	
			4·5	VII		3	100	3		5
Hepatocellular carcinoma										
7	M	73	7·0	VII–VIII	—	4	100	12	—	24
8	M	71	10·0	II–IV	1	5	80	Not destroyed	1	6

ever, as cryosurgery is still employed only via laparotomy[5], PHCT was developed as an analogous minimally invasive approach to cryodestruction.

In all patients PHCT of at least 80 per cent of the tumour volume could be performed, with no complications such as bleeding or bile duct injury which have been reported after cryosurgery and liver resection.

With this experience, the most important criterion for successful PHCT was excellent visualization of the tumour by ultrasonography before and during the procedure, guaranteeing optimal location of the cryoprobes, which also helped to avoid injury to surrounding liver structures. Adhesions between liver and peritoneum are favourable factors, ensuring a permanent sonographic imaging and reducing the risk of haemorrhage into the abdominal cavity.

Acknowledging that the number of patients was very small and that the mean length of surveillance was much too short, this series suggests that in a selected group of patients with irresectable liver tumours, percutaneous cryotherapy is an advantageous and effective alternative to open cryosurgery or alcohol injection and laser-induced thermotherapy

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Experimental study of electrolysis-induced hepatic necrosis

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Background One of the most promising but unexplored methods for treating patients with irresectable liver tumours is electrolysis. This study examined the effect of increasing 'current dose' on the volume of the lesion induced in normal rat liver.

Methods A direct current generator, connected to platinum electrodes implanted in the rat liver, was used to examine the effect of (1) varying current doses from 1 to 5 coulombs and (2) electrode separation (2 or 20 mm), on the volume of liver necrosis.

Results There was a significant correlation ($P < 0{\cdot}001$) between the current dose and the volume of necrosis produced for each electrode separation. Placing the electrodes 2 mm apart resulted in smaller total volumes of necrosis than placing them 20 mm apart when anode lesions were significantly larger than cathode lesions ($P < 0{\cdot}05$). Liver enzymes (aspartate aminotransferase, alanine aminotransferase) were significantly raised 1 day after treatment ($P < 0{\cdot}001$) and predicted the total volume of hepatic necrosis ($P < 0{\cdot}001$).

Conclusion Predictable and reproducible areas of liver necrosis are produced with electrolysis. If these results extrapolate to larger animal models, this technique has potential for patients with irresectable primary and secondary liver tumours.

Primary and secondary liver tumours represent a significant problem worldwide both numerically and socioeconomically. Presently only surgical resection offers the potential for cure with between a quarter and a third of patients surviving 5 years[1,2]. Unfortunately only a relatively small number of patients (less than 10 per cent) are suitable for surgery[3] and the remaining 90–95 per cent have a dismal outlook[4] with a median survival of approximately 6 months[5–7].

A number of different non-resectional approaches have been investigated including percutaneous alcohol injection[8], instillation of specific toxins[9,10], cryotherapy[11], laser thermotherapy[12], both regional and systemic chemotherapy[13], and liver transplantation[14]. These methods have all been shown to be invasive or clinically unreliable and none has conferred a reproducible long-term survival advantage, although several are useful as palliation[4,15,16].

Electrolysis is a simple and extensively investigated electrochemical phenomenon with a negligible thermal effect[17,18]. Potentially it fulfils all of the criteria for safe tissue destruction which would allow its clinical application to liver lesions. The effect is produced by direct current (DC) generated between a pair (or more) of electrodes designated anode and cathode. When current is applied in human plasma, sodium hydroxide and hydrogen are produced at the cathode and hydrochloric acid, oxygen and chlorine gas at the anode[19–23]. This results in a significant pH gradient between the electrodes producing a fiercely cytotoxic local environment and a resulting well defined pattern of cell necrosis[24,25]. The situation is considerably more complex *in vivo*, however, and a direct effect of the DC on ionic transport systems, capillary circulation and movement of immunologically competent cells have all been hypothesized[26].

Animal experiments have been conducted to examine the effects of electrolysis in the mouse[18,21], rat[22,27–29], rabbit[17], and pig[20,30–34]. These studies which started in the mid-1970s were followed by clinical studies in a small number of patients with pulmonary lesions[35–37] and more recently reports from China of the treatment of liver tumours[38,39]. This new treatment modality nevertheless remains in its infancy and considerable evaluation of the basic physiological changes induced and the best method of current delivery are required before its widespread clinical introduction.

This study examined the effect of variations in current dose and electrode separation on the volume of hepatic necrosis and resultant liver enzyme derangement in the normal rat liver.

Materials and methods

A DC generator was designed to deliver a preset current dose (coulombs = current (amperes) × time (seconds)). Automatic voltage adjustment between 1 and 25 V allowed a preset rate of current delivery (variable between 1 and 100 mA) regardless of alterations in hepatic parenchymal resistance during treatment. Anode and cathode electrodes were identical and constructed from fine platinum wire (0·5 mm diameter), which was electrically insulated using a semirigid plastic sleeve. Two millimetres of uninsulated electrode was exposed at the tip producing an effective electrode surface area of 3·34 mm^2.

The use of laboratory animals in this study was approved by local animal ethics committees (University of Adelaide and The Queen Elizabeth Hospital, Adelaide) and conformed with the 'Code of practice for the care and use of animals for scientific purposes' (NHMRC/CSIRO/AAO 1990) and The Prevention of Cruelty to Animals Act 1985.

Fifty Wistar-WAG male rats (210–320 g) obtained from the Animal Resources Centre (Perth, Australia) were divided into

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two groups of 25 according to the separation of the anode and cathode. In group 1, the electrodes were both placed in the same lobe of the liver with the tips separated by 2·0 mm. In group 2, the electrodes were inserted into different lobes of the liver (right and left) 20 mm apart. Under standard halothane/nitrous oxide anaesthesia and aseptic conditions, the liver was exposed through a midline incision and delivered through the wound. Electrodes were inserted into the liver parenchyma to a depth of 5 mm and supported during the electrolysis using a gantry-type frame designed to allow atraumatic electrode movement with respiration.

For each animal the preset combination of coulombs and milliamps was then delivered by the DC generator (1–5 coulombs, delivered at 1–5 mA). In two groups of four control animals, electrodes were implanted as in groups 1 and 2 and connected to the DC generator, but no current was passed between the electrodes. To control for the varying treatment times in groups 1 and 2, the electrodes were left *in situ* for 10, 30, 60 or 90 min. All animals were killed after 48 h.

Blood samples were analysed before operation for levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, γ-glutamyltranspeptidase and bilirubin (Technicon AXON analyser, Bayer Health Care, Pymble, Australia). The results were compared with those taken at completion of the electrolysis, 24 h later and at the time of death.

After the experiment the livers were removed and fixed in 10 per cent buffered formalin. After 2 weeks the liver was sectioned into slices 1 mm thick (*Fig. 1a*). The three maximum diameters (D1–3) at right angles to each other of the lesion at each electrode site were then measured, using a micrometer, by two independent observers with no knowledge of the dose used to create the lesion. The mean of the two observers' values for D1–3 were calculated. As these measurements were often slightly different, the volume of each lesion was then calculated using the formula for an ellipsoid rather than a sphere: volume = $4/3\pi(R1 \times R2 \times R3)$, where $R1 = D1/2$ etc.

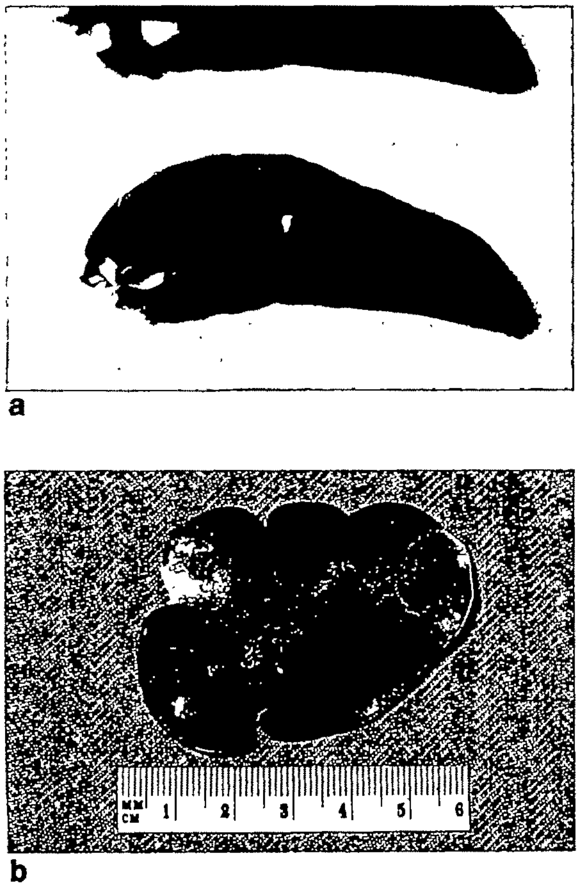

Fig. 1 a Liver section 1 mm thick, taken through the centre of an electrolytic lesion before measurement. This lesion was produced using 5 coulombs. b Yellow wedge infarcts peripheral to the grey, circular 'primary' electrolytic lesions (electrodes separated)

In most animals there was also a wedge of secondary ischaemic necrosis peripheral to the 'primary' electrolytic lesion at the site of electrode implantation (*Fig. 1b*). This area of secondary necrosis was also measured and its volume was calculated.

Blocks of liver containing the electrolysis-induced lesions were processed, embedded in paraffin, sectioned and stained with haematoxylin and eosin. Coded sections were examined by a hepatopathologist (P.H.).

Results were analysed statistically using the unpaired *t* test and regression analysis (Statworks, version 1.2; Cricket Software, Philadelphia, Pennsylvania, USA).

Results

All animals tolerated the treatment well and made a good postoperative recovery. No animal died prematurely. In the control groups the site of electrode placement could barely be discerned macroscopically and there was no evidence of any 'lesion'.

Group 1 (electrode tips 2 mm apart)

There was a significant correlation between the volume of the 'primary' electrolytic lesion and the number of coulombs delivered ($P < 0.001$) (*Fig. 2*). The relationship was linear although variability increased with the number of coulombs. The rate at which the treatment was given (1–5 mA) had no significant effect on this relationship.

At autopsy, all 25 animals were found to have not only a 'primary' electrolytic lesion but also a variable amount of 'secondary' ischaemic necrosis peripherally (*Figs 1a* and *1b*). There was no significant correlation between the volume of the 'secondary' lesion and either the number of coulombs delivered or the current flow (milliamperes). There were significant correlations between the total

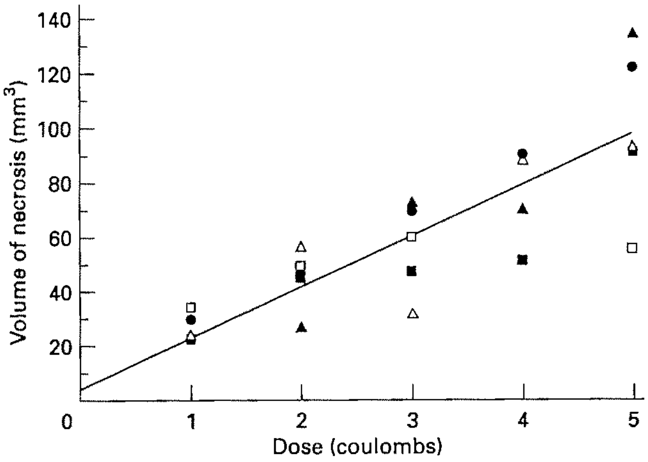

Fig. 2 Correlation between the volume of the 'primary' electrolytic lesion and the number of coulombs delivered with the electrodes placed 2 mm apart ($r^2 = 0.804$, $P < 0.001$). Current delivery was preset at 1 mA (■), 2 mA (□), 3 mA (△), 4 mA (●) and 5 mA (▲) determining the time over which each dose was delivered

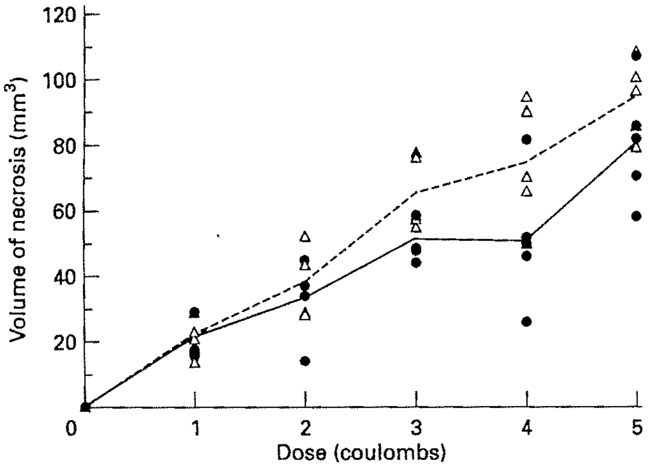

Fig. 3 Correlation between the volume of the 'primary' electrolytic lesion and the number of coulombs delivered with the electrodes placed 20 mm apart. Δ, Values for anode; -----, mean for each dose ($r^2 = 0{\cdot}875$, $P < 0{\cdot}001$). ●, Values for cathode; —, mean ($r^2 = 0{\cdot}742$, $P < 0{\cdot}001$)

volume of necrosis produced ('primary' plus 'secondary' lesion) and the 24-h increase in levels of AST ($r^2 = 0{\cdot}693$, $P < 0{\cdot}001$) and ALT ($r^2 = 0{\cdot}720$, $P < 0{\cdot}001$).

Group 2 (electrode tips 20 mm apart)

There was a significant correlation ($P < 0{\cdot}001$) between the number of coulombs delivered and the volume of the lesions produced at both the anode and the cathode (*Fig. 3*), although the slope of these lines was different. The line for the anode was always steeper than that of the cathode and at both 3 and 4 coulombs lesions were significantly larger ($P < 0{\cdot}05$). The rate at which the treatment was given (milliamperes) did not affect this relationship. Twenty of the 25 animals were found to have a wedge-shaped secondary infarct peripheral to the 'primary' lesions in one (seven) or both (13) lobes. There was no significant correlation between the volume of this 'secondary' lesion and either the number of coulombs delivered or the current flow (milliamperes). There were again significant correlations between the total volume of necrosis produced ('primary' plus 'secondary' anode and cathode lesions) and the 24-h increase seen in the liver enzymes AST ($r^2 = 0{\cdot}587$, $P < 0{\cdot}001$) and ALT ($r^2 = 0{\cdot}578$, $P < 0{\cdot}001$).

Histological examination of the specimens confirmed the results of the macroscopic study with the size of the lesions increasing with the electrolytic 'dose'. In each specimen, an area of tissue destruction was observed at the site of the electrode tips and was clearly discernible from the 'primary' and 'secondary' lesions which were areas of coagulative necrosis (*Fig. 4*). There was evidence of vascular thrombosis in the vessels adjacent to the lesions. The necrotic tissue was sharply demarcated from immediately adjacent normal liver; a mild infiltrate of mononuclear cells and small numbers of proliferating fibroblasts indicated that a healing process had commenced at the junction between the necrotic and normal liver.

None of the livers from the control rats showed a 'primary' or 'secondary' lesion, as described above. However, small localized areas of tissue necrosis were seen microscopically at the site of entry of the electrodes.

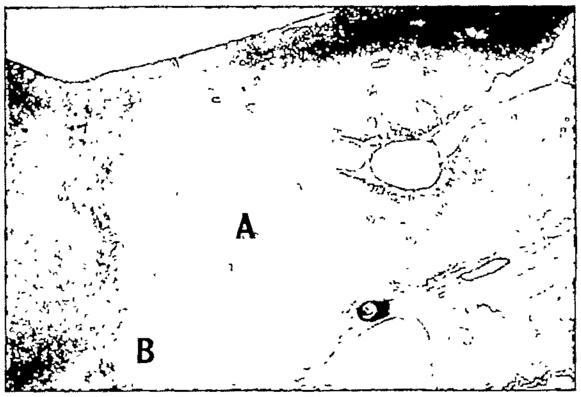

Fig. 4 Photomicrograph of tissue destruction seen at the site of the electrode tip, surrounded by a zone of coagulative necrosis – the 'primary' lesion (A). A peripheral zone of 'secondary' necrosis is located between the 'primary' lesion and the adjacent normal liver (B). Haematoxylin and eosin stain; objective × 4

Discussion

For any new treatment modality to become established in clinial practice, it must be shown to be safe and efficacious. Previous unpublished work by the authors demonstrated that electrolysis produced areas of hepatic necrosis in the normal rat liver which healed without complications over 6 months, contracting down to a small fibrous scar. There was no long-term alteration in liver function or associated morbidity or mortality rates in any of the 58 rats in this previous study.

If the results of treatment of liver tumours in a clinical situation are to be associated with similar minimal morbidity and mortality rates the dose–response relationship as well as the healing process need to be predictable and reproducible. Dose–response data available to date have been remarkably limited and apparently variable. In studies on the pig lung, approximate rates of necrosis varied between 0·4 and 1·7 cm^3 per 100 coulombs delivered, dependent on electrode type and positioning[20,30]. In human studies in lung tumours this rate varied between 1·5 and 7 cm^3 per 100 coulombs[33,35]. More recently, Chinese workers reported a rate of 1·0 cm^3 per 100 coulombs in treating a variety of tumours[40,41]. In the liver, one study has reported experimental dose–response data[17] and the results suggested that liver necrosis in the rabbit was produced at a rate of 2·4 cm^3 per 100 coulombs compared with the rate of 4·1 cm^3 for lung necrosis. If the relationship between dose in coulombs and response in terms of volume of necrosis in the primary electrolytic lesion remained linear, the present results suggest that a dose of 100 coulombs would create a 2·0-cm^3 lesion with the electrodes together; if they were apart a 2·0-cm^3 lesion would be created at the anode and a 1·4-cm^3 lesion at the cathode. While all of these results appear reassuringly similar, Chinese workers[38,39] have reported a rate of destruction between 200 and 300 times that which the present authors and Samuelsson *et al.*[17,30] observed (485–837 cm^3 per 100 coulombs) in patients with larger hepatocellular carcinomas.

It is clear therefore that while the present data support the observation that the volume of electrolytically-induced liver necrosis is proportional to the current dose in small-volume lesions in normal liver, further studies in a large animal model such as the pig are needed to extrapolate these results and allow their application to the size of liver lesions encountered in the clinical situation. The phenomenon of peripheral ischaemic damage may be unique to the rat liver model used, in which vascular thrombosis created by the relatively large electrolytic lesion results in extensive but variable distal ischaemic necrosis within the relatively small lobe of the rat liver. The flow of blood through such vessels in larger animals would be expected to mitigate such effects.

Further work will also be necessary to apply the observation that the combined volume of necrosis when the electrodes are separated by 20 mm is nearly twice that when the electrodes are together[20,30]. This effect seems likely to be the result of mixing of the electrode products to reform water and sodium chloride when the electrode tips are adjacent, thereby reducing the overall cytotoxic effect[26]. The cathode appears to be less toxic than the anode and the acidic environment around the anode (pH 2) is known to be more toxic than the alkalinity (pH 12) at the cathode[26].

In addition to the placement of electrodes, it is likely that the shape and size of the electrodes will also contribute to the shape and size of the final lesion produced. This is currently under investigation using computer 'current modelling' techniques to allow standardization of various critical aspects of electrode design and placement which will be necessary for safe clinical studies. The observation that the time over which the current dose is delivered does not appear to alter the size of the lesion created similarly requires further validation in view of its importance in determining treatment times.

In conclusion, if, as seems likely from the work of others, the present results can be extrapolated, electrolysis (electrochemical therapy) appears to fulfil many of the criteria required to allow the potentially curative treatment of irresectable liver tumours.

Acknowledgements

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Intrahepatic peripheral cholangiocarcinoma: mode of spread and choice of surgical treatment

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Background Classification of macroscopic appearance and standard operative procedures for intrahepatic cholangiocarcinoma (ICC) are still controversial.

Methods The mode of spread of 12 resected ICCs was examined by light microscopy, and the appropriate operative procedures for the various tumours were considered.

Results Macroscopically, nine tumours were classified as mass-forming type and three as periductal infiltrating type. All patients were treated by major hepatectomy; resection of the extrahepatic bile duct was included in two cases of the periductal infiltrating type. Microscopically, invasion into the portal vein, intrahepatic metastasis and perineural or lymphatic vessel invasion occurred in none, one and all of three tumours of the periductal infiltrating type and in eight, six and six of nine tumours of the mass-forming type.

Conclusion ICC of the periductal infiltrating type has a tendency to spread along Glisson's sheath via lymphatic vessels. By contrast, ICC of the mass-forming type tends to invade the liver via the portal vein system; such tumours begin to invade Glisson's sheath through the lymphatic vessels when the tumour has increased in size. Therefore, major hepatectomy with combined resection of the extrahepatic bile duct should be performed for all ICCs of the periductal infiltrating type and for those of the mass-forming type with invasion of Glisson's sheath.

Among neoplasms that originate in the liver, intrahepatic cholangiocarcinoma (ICC) is rarer than hepatocellular carcinoma (HCC), accounting for 5·4 per cent[1] to 9·5 per cent[2] of malignant neoplasms of the liver. The prognosis of ICC has been unsatisfactory because the local and regional spread of the tumour at diagnosis allows only low rates of resectability.

Various classifications of ICC in terms of gross appearance have been proposed. Eggel[3] classified primary liver cancers into three types according to their gross appearance: nodular, massive and diffuse. Furthermore, some investigators have classified ICCs as being either of the mass-forming or the infiltrating type[4,5]. In 1994, a new classification was proposed by the Liver Cancer Study Group of Japan, with tumours being classified as being of the mass-forming, periductal infiltrating or intraductal growth types.

The local and regional spread of ICC has been studied; the neoplastic cells can spread into the liver by peripheral portal flow and into the extrahepatic bile duct and lymph nodes through lymphatic flow along Glisson's sheath[6]. However, the characteristic pattern of spreading of the tumour in each type of ICC remains to be determined. Furthermore, only a few studies have considered the operative procedures appropriate for treatment of subtypes of ICC[4,5].

In the present study, the mode of spread of ICC was investigated histologically and related to the macroscopic classification of each tumour.

Patients and methods

From April 1985 to March 1996, 37 patients with cholangiocarcinoma of the liver were treated in this department. Patients with tumours of the hilar type that originated from the right or left hepatic duct were excluded from the study. Twelve patients underwent hepatic resection, with clinicopathological investigations. There were no cases of associated parasitic infection, primary sclerosing cholangitis, biliary atresia or thorotrast.

The tumours were classified, according to gross appearance, as proposed by the Liver Cancer Study Group of Japan (unpublished), as being of the mass-forming type, the periductal infiltrating type and the intraductal growth type. Each type was defined as follows: mass-forming type, a nodular tumour with a relatively clear margin (*Fig. 1*); periductal infiltrating type, a non-nodular tumour extending mainly along the intrahepatic bile duct (*Fig. 2*); and intraductal growth type, a papillary or granular

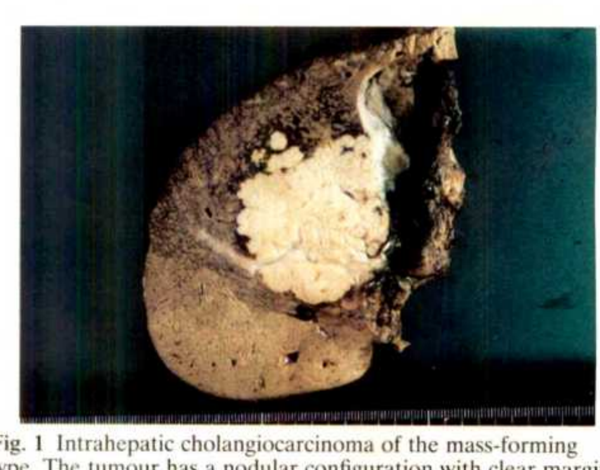

Fig. 1 Intrahepatic cholangiocarcinoma of the mass-forming type. The tumour has a nodular configuration with clear margins. Intrahepatic metastasis is visible

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POSSUM and Portsmouth POSSUM for predicting mortality

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Background There is a need for an accurate measure of surgical outcomes so that hospitals and surgeons can be compared properly regardless of case mix. POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) uses a physiological score and an operative severity score to calculate risks of mortality and morbidity. In a previous small study it was found that Portsmouth POSSUM (P-POSSUM; a modification of the POSSUM system) provided a more accurate prediction of mortality.

Methods Some 10 000 general surgical interventions (excluding paediatric and day cases) were studied prospectively between August 1993 and November 1995. The POSSUM mortality equation was applied to the full 10 000 surgical episodes. The 10 000 patients were arranged in chronological order and the first 2500 were used as a training set to produce the modified P-POSSUM predictor equation. This was then applied prospectively to the remaining 7500 patients arranged chronologically in five groups of 1500.

Results The original POSSUM logistic regression equation for mortality overpredicts the overall risk of death by more than twofold and the risk of death for patients at lowest risk (5 per cent or less) by more than sevenfold. The P-POSSUM equation produced a very close fit with the observed in-hospital mortality.

Conclusion P-POSSUM provides an accurate method for comparative surgical audit.

Mortality is an important and objective measure of outcome. To provide meaningful comparative audit between different populations, measures of outcome must include methods to accommodate for differences in case mix.

POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) was first described by Copeland *et al.*[1] in 1991 as a method for normalizing patient data so that direct comparisons of patient outcome could be made despite differing patterns of referral and population. Sagar *et al.*[2–4] have described the use of POSSUM for comparative audit purposes. Copeland *et al.*[1] originally assessed 48 physiological factors and 14 operative and postoperative factors for each patient. Using multivariate analysis techniques these were reduced to 12 physiological and six operative factors, which are summarized in *Table 1*. They pointed out that all hospitals in the UK have the ability to collect the POSSUM dataset without difficulty. These two scores are then inserted into two formulas[1] and risks of both morbidity and mortality can be predicted for the workload of each surgical team. The actual morbidity and mortality rates reported by a surgical team can then be compared to these predictions and individual patients who do not conform can be identified for close inspection at audit meetings.

The POSSUM mortality equation (1) as published by Copeland *et al.*[1] is $\ln[R/(1-R)] = -7{\cdot}04 + (0{\cdot}13 \times \text{physiological score}) + (0{\cdot}16 \times \text{operative severity score})$, where R is the predicted risk of mortality and is in the standard form of equation as produced by logistic regression.

To date no detailed method of the application and analysis of POSSUM as described by Copeland *et al.*[1] has been published. These authors make considerable use of receiver–operator characteristic curves, which implies the use of a cut-off level in predicting an event (in this case death). However, the logistic regression equation ascribes a risk of mortality to each individual and it should be possible to look at its accuracy for appropriate population groupings rather than assuming all individuals with a risk of mortality above a given arbitrary level are predicted as dying. An initial trial of POSSUM involving 1485 patients[5] was performed and used published methods for the application and analysis of logistic regression models[6–9]. The POSSUM mortality equation was found to overpredict deaths by a factor greater than 2. This overprediction was greatest (by sixfold) amongst low-risk patients (those with a risk of mortality of 10 per cent or less), who form the majority of general surgical patients in a district general hospital setting. The approach was then modified using the above standard methods to obtain a logistic regression model that fitted well with the observed mortality.

Table 1 POSSUM physiological and operative parameters

Physiological parameters	Operative parameters
Age	Operative severity
Cardiac history	Multiple procedures
Respiratory history	Total blood loss
Blood pressure	Peritoneal soiling
Pulse rate	Presence of malignancy
Glasgow Coma Score	Mode of surgery
Haemoglobin level	
White cell count	
Urea concentration	
Na^+ level	
K^+ level	
Electrocardiography	

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To differentiate it from POSSUM as described by Copeland *et al.*[1], the modified method of applying POSSUM is termed Portsmouth POSSUM (P-POSSUM). Whilst using the physiological and operative scoring methods described by Copeland *et al.*[1], the modification uses recognized methods to obtain the logistic regression equation for mortality and to apply it to the population being studied.

In the previous study[5] the P-POSSUM equation obtained was applied only retrospectively to its training set since there were insufficient data to apply the equation prospectively. As the results of the initial study were encouraging, it was decided to embark on a larger-scale study, the results of which are presented here.

As in the previous study the testing of the POSSUM equation was limited to mortality alone to avoid the extra difficulties of defining morbidity and uncertainty regarding the completeness of complications data.

Patients and methods

All patients, except paediatric and day surgical unit cases which both have units within the hospital, admitted under the care of the general surgeons within the study period (August 1993 to December 1995) were entered prospectively into the study database written for this project in FoxPro (Microsoft, Seattle, USA).

Special clerking, operation and discharge sheets had been designed for the initial trial[5] which included appropriate spaces for all the physiological and operative data items required for POSSUM scoring. These sheets had been found generally useful in their own right and their use was continued in this study. The physiological data were entered on the sheets by the house staff at admission, or when the results of tests were available. Patients who went to surgery at any time during their stay had the operation sheet completed by the surgeon at the end of surgery. On discharge, or death, the discharge sheet was completed. An audit clerk collected the physiological and operative data from the sheets and entered them into the database. The audit clerks were responsible for ensuring completeness of the data.

As POSSUM requires an operative severity score, only patients who underwent operative intervention were included in this study and the only endpoint studied was in-patient mortality.

Results

As no detailed methods for applying the Copeland POSSUM mortality equation have been published, standard methods of analysis have been used. Frequency tables were compared by means of the χ^2 test, using the methods described by Hosmer and Lemeshow[6–9] as appropriate.

In *Tables 2, 3* and *5* the sizes of the risk ranges have been chosen to be meaningful, to give approximately equal numbers of predicted deaths and to give a predicted number of deaths greater than 5 in all risk ranges. For a given range of risk, the number of operations within that range is given together with the mean risk for these operations and the predicted number of deaths (number of operations × mean risk). This is compared with the actual number of deaths occurring.

Table 2 POSSUM – all 10 000 cases

Range of predicted mortality rate (%)	Mean predicted risk of mortality (%)	No. of operations	Predicted deaths	Reported deaths
>0 to ≤5	2·26	7034	159	22
>5 to ≤15	8·49	1879	160	68
>15 to ≤50	26·25	866	227	120
>50 to ≤100	68·14	221	151	77
>0 to ≤100	6·97	10000	697	287

$\chi^2 = 359·70$, 4 d.f., $P = 0·0000$

Table 3 Portsmouth POSSUM – first training set of 2500 cases

Range of predicted mortality rate (%)	Mean predicted risk of mortality (%)	No. of operations	Predicted deaths	Reported deaths
>0 to ≤5	0·96	2208	21	15
>5 to ≤15	8·43	198	17	28
>15 to ≤50	26·10	78	20	19
>50 to ≤100	61·60	16	10	6
>0 to ≤100	2·72	2500	68	68

Data are shown in this format for comparison with other tables

Table 4 Portsmouth POSSUM – prospective groups of 1500

Group	Mean predicted risk of mortality (%)	Predicted deaths	Reported deaths
2501–4000	3·10	47	43
4001–5500	3·03	45	46
5501–7000	3·24	49	41
7001–8500	3·27	49	47
8501–100000	2·72	41	42

$\chi^2 = 1·63$, 5 d.f., $P = 0·90$

Table 5 Portsmouth POSSUM – last 1500 patients

Range of predicted mortality rate (%)	Mean predicted risk of mortality (%)	No. of operations	Predicted deaths	Reported deaths
>0 to ≤5	0·99	1331	13	13
>5 to ≤15	8·24	121	10	13
>15 to ≤50	26·49	37	10	9
>50 to ≤100	70·60	11	8	7
>0 to ≤100	2·72	1500	41	42

$\chi^2 = 1·35$, 4 d.f., $P = 0·85$

The POSSUM mortality equation (1) as published by Copeland *et al.*[1] was applied to the 10 000 sets of data and the results are shown in *Table 2*. Inspection of *Table 2* shows a significant lack of fit ($\chi^2 = 359·70$, 4 d.f., $P = 0·0000$).

Given this poor fit, logistic regression was performed on the first 2500 (chronologically) of the dataset using the BMDP package (Los Angeles, California, USA) of biomedical statistical software[10] to obtain the following predictor equation (2) for mortality: $\ln[R/(1-R)] = -9·065 + (0·1692 \times \text{physiological score}) + (0·1550 \times \text{operative severity score})$, where R is the predicted risk of mortality.

The Hosmer–Lemeshow test (which involves grouping the dataset in deciles) as reported by BMDP revealed no significant lack of fit ($\chi^2 = 7{\cdot}65$, 8 d.f., $P = 0{\cdot}47$). Equation 2 gives results very similar to those of the regression equation formed in the trial study[5].

Table 3 shows the results of applying equation 2 to its training set (the first 2500 patients) in the same format as *Tables 2* and *5* to allow easy comparison. The total predicted and reported deaths are constrained to be the same since the equation is being applied to the data from which it was derived.

Table 4 shows the prospective application of equation 2 to the remaining 7500 patients in the dataset. The 7500 cases have been divided chronologically into groups of 1500 (similar in size to the original study group as used by Copeland *et al.*[1]). Predicted deaths show close agreement to those observed ($\chi^2 = 1{\cdot}63$, 5 d.f., $P = 0{\cdot}90$).

Table 5 shows the prospective application of equation 2 to the last group of 1500 in the 10 000 patients in the study, and breaks the data down into risk groups following *Table 1*. These data were collected approximately 18 months to 2 years after the data from which the equation was derived. There is no evidence of any significant lack of agreement ($\chi^2 = 1{\cdot}35$, 4 d.f., $P = 0{\cdot}85$). Similar results were found for the other (earlier) prospective groups

Discussion

It is well recognized that there is a need for an accurate system for predicting mortality and morbidity against which outcomes can be compared. It was considered that POSSUM, which amalgamates a physiological score with an operative severity score to give a risk of mortality and morbidity, was potentially a useful system, recognizing that measurements of physiological status alone, for example Acute Physiology And Chronic Health Evaluation (APACHE), are not necessarily appropriate for surgical patients as they do not take into account the severity of the surgical intervention. This study was limited to mortality because it is of greater importance and much more objective than morbidity. As in the initial study[5], hospital mortality was used as the endpoint rather than 30-day mortality because the extra work involved was not feasible given the small number of deaths that might have been involved.

POSSUM does not directly take into account factors such as differences between surgeons, anaesthetists and operating time, which might be expected to have considerable influence on the outcome, but these differences in surgical care, and hence perhaps outcome, are intended to be highlighted by POSSUM. The diagnosis is not included but is subsumed in the physiological state of the patient and in the operative findings, particularly in respect of malignancy. Whilst, theoretically, the operative severity score will be influenced by the degree of peritoneal soiling and blood loss, both of which may be influenced by lack of surgical expertise, in practice these variables were not found to be significant.

It was found that no methodology of applying the POSSUM mortality equation to a given population had been published. Therefore, standard methods from the logistic regression literature were used both to apply the equation and to measure its goodness of fit to the population being modelled[6–9]. In doing so it was found that the POSSUM mortality equation considerably overestimated deaths, particularly for the lowest risk group (by more than sevenfold). This is potentially dangerous; the application of a model that overpredicts mortality could easily give rise to a false sense of security and poor outcomes would be hidden.

To derive a more accurate predictor equation standard methods were used to generate a logistic regression equation from the first quarter of the data. This equation was applied successfully to its training set and prospectively to the remainder of the dataset, covering a period of 2 years. This method of obtaining and applying the predictor equation and presenting the results is transparent and intuitive. This process is termed P-POSSUM. Certain other aspects of POSSUM scoring invite further comment.

The lowest physiological and operative scores are 12 and 6 respectively, which when applied to the POSSUM mortality predictor equation give a minimum risk of death of 1·1 per cent[11]. This is far too high given that it represents the fittest individual undergoing the most minor surgery, and previously published series of fit people undergoing uncomplicated hernia repairs suggest that mortality rates are less than one in 100 000 (0·001 per cent)[12,13]. The P-POSSUM mortality equation (2) gives a minimum risk of mortality of 0·2 per cent. Whilst more acceptable, this is probably still too high. This value is subject to the statistical nature of logistic regression. It may well be that effectively zero risk should be assigned to individuals with risks below some cut-off level, but further work is required to determine whether this is appropriate.

To date this study has concentrated on mortality because this is a far more objective outcome than morbidity, and hence easier to record. A universally accepted definition of what constitutes a complication (even within one surgical team) is remarkably difficult to achieve.

Within the local surgical environment P-POSSUM is an effective tool for modelling workload and outcomes in terms of mortality. Equation 2 has been successfully applied prospectively to data collected 2 years after the data that were used to derive the equation. Other independent workers in the UK have also applied the P-POSSUM method and obtained results that agree with those presented here[14]. This suggests that P-POSSUM works independently of geographical location.

In conclusion, it seems possible that a system based on the POSSUM physiological and operative severity scores using the modified P-POSSUM method of analysis could become a standard method of calculating expected outcomes against which observed outcomes may be measured, using, as it does, simple clinical data only.

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D-lactate as an early marker of intestinal ischaemia after ruptured abdominal aortic aneurysm repair

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Background Patients with a ruptured abdominal aortic aneurysm (AAA) are at risk of developing colonic ischaemia after surgery. It is difficult to diagnose this ischaemia at an early stage. D-lactate is produced by intestinal bacteria after ischaemia. L-lactate is released in increased amounts during hypoxia by anaerobic metabolism. This study investigated both variables as a marker for intestinal ischaemia in patients with a ruptured AAA.

Methods Twenty-four patients with ruptured AAA were divided retrospectively into two groups with and without ischaemic complications, as verified by colonoscopy. Blood had been taken on admission to the intensive care unit (ICU). Median time to colonoscopy was 9 days after surgery. As controls, four patients with pneumonia, six healthy subjects, five patients with an elective AAA repair, and six patients with sepsis and acute tubular necrosis were included.

Results D-lactate level on admission was significantly increased in patients with colonic ischaemia after ruptured AAA compared with the level in patients without ischaemia ($P < 0{\cdot}05$), patients with sepsis ($P < 0{\cdot}001$), those with pneumonia and healthy subjects ($P < 0{\cdot}01$). L-lactate concentration was similar in the group with intestinal complications and in patients without colonic ischaemia; however, L-lactate levels were higher in patients with pneumonia and sepsis than in healthy subjects ($P < 0{\cdot}05$).

Conclusion On admission to the ICU, D-lactate, but not L-lactate, levels may predict later colonic ischaemia following repair of a ruptured AAA.

After repair of a ruptured abdominal aortic aneurysm (AAA), patients are at risk of developing colonic ischaemia due to the preceding hypoperfusion of the intestine as a result of the systemic shock and aortic clamping. Furthermore, loss of flow to the colon via the inferior mesenteric artery and/or loss of flow via one or both internal iliac arteries may contribute. The overall complication rate following repair of a ruptured AAA averages about 50 per cent[1]. Gastrointestinal and systemic problems encountered by these patients range from diarrhoea (43 per cent)[2] to ischaemic colitis (27 per cent)[3,4], bowel necrosis (2–35 per cent)[5] or overt sepsis with organ failure (20 per cent)[6]. The mortality rate associated with these complications is as high as 75 per cent[7], up to 90 per cent in patients with transmural involvement of the colonic wall[8]. Early surgical intervention in the acute phase and improved preoperative and postoperative care reduces this complication rate[9].

The diagnosis of colonic ischaemia after aneurysm repair is difficult, because of the non-specific clinical signs in the early phase. In most patients colonic ischaemia is recognized only when the patient has extensive colonic necrosis or sepsis which results in a mortality rate of 54 per cent[10].

Colonoscopy is the best method for diagnosing colonic ischaemia but this technique is invasive and is usually performed only in patients with overt signs of bowel ischaemia[11]. The measurement of gut intramucosal pH may be useful, but the cost of monitoring patients with a tonometry catheter is high[2,12]. A serum marker of colonic ischaemia may be more useful, but at present no marker has been found that is sensitive or specific enough. Lactate has been studied in the diagnosis of acute abdominal disease[13]. L-lactate is produced by all cells as a product of glycolysis in a balanced equilibrium during adequate oxygen supply[14]. During hypoxia or flow arrest, lactate is produced in excess and is released into the bloodstream. However, the lactate produced by the gut is largely extracted by the liver[15]. Raised L-lactate levels are therefore related to inadequate tissue perfusion, but measurement may be limited by several confounding factors.

The stereoisomer D-lactate is produced only by bacteria as a normal product of bacterial fermentation[16]. The exact mechanism by which D-lactate enters the bloodstream is unknown, but baseline levels in healthy subjects are very low. Under certain conditions, however, the number of bacteria can increase rapidly, correlating with an increased level of D-lactate. This has been described in patients with bacterial overgrowth due to infection[16], short bowel syndrome[17] and mesenteric infarction causing colonic ischaemia[18].

It is not known whether acute surgical intervention for ruptured abdominal aneurysm causes a rise in serum D-lactate concentration, and whether plasma levels are diagnostic for colonic ischaemia.

In this study patients with colonic ischaemia after ruptured AAA repair were compared with patients who had the same surgical procedure without this complication. It was hypothesized that the measurement of D-lactate concentration immediately after operation on arrival in the intensive care unit (ICU) may be a better marker for colonic ischaemic complications than L-lactate.

Patients and methods

The patients were selected from a prospectively acquired database of all those admitted to the ICU from January 1990 to

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March 1994. Eighty-two patients were admitted to the ICU after surgery for AAA. Of these, 24 patients with a ruptured AAA were selected. The patients were included if sufficient clinical data were available and if plasma samples had been taken on ICU admission.

Several patient groups were selected as controls. First, six healthy subjects were used for baseline measurement of D-lactate. As a control group for critically ill patients without colonic ischaemia, six patients admitted for pneumonia in need of ventilatory support were used. A further group consisted of five patients undergoing elective AAA repair. The majority of patients following elective AAA repair are not admitted to the ICU in this institution; these selected patients were therefore at risk of developing complications. Finally, a group of six patients with abdominal septic shock and acute tubular necrosis who did not undergo aneurysm surgery was selected, because of the frequent relation between this condition and colonic ischaemia after a ruptured AAA[6]. All the patients with aneurysm were compared haemodynamically in relation to the presence of presurgical shock (mean arterial pressure (MAP) less than 70 mmHg), the duration of aortic clamping, the lowest MAP during surgery and estimated blood loss during the procedure.

Patients with ischaemic colitis, confirmed by endoscopy, were allocated retrospectively to the ischaemic group. Colonic ischaemic changes were divided into three categories, as described by Hagihara *et al.*[19].

D-lactate concentration was determined from serum collected after operation on admission to the ICU. The sample was mixed with ethylenediamine tetra-acetic acid, centrifuged at 4°C at 1500 r.p.m. for 20 min, and 4 ml of plasma was stored at −70°C until measurement.

After thawing plasma was deproteinized with perchloric acid (1:1 vol), mixed thoroughly, and kept on ice for 30 min, after which the supernatant solution was removed. This was mixed with a nicotinamide adenine dinucleotide $(NAD)^+$–glycine–hydrazine solution to form pyruvatehydrazon with reduced NAD (NADH) and H^+, at a pH of less than 9·0. This reaction was initiated by adding D-lactate dehydrogenase (D-LDH). The perchloric acid was not mixed at the time of collection, as described before, but at the time of measurement after storage[20]. Both techniques yielded similar D-lactate levels (standard error of differences 0·01)[20].

For quantification of L-lactate in serum, the same technique was used as described above, but with replacement of the D-lactate standard and D-LDH by L-lactate and L-LDH. D-lactate levels of less than 0·1 mmol/l and L-lactate levels of less than 2·0 mmol/l were considered to be normal.

Data are presented as mean(s.d.) or percentages. Student's *t* test and the χ^2 test were used to determine statistical differences between groups. Sensitivity and specificity were calculated according to standard methods. $P<0{\cdot}05$ was considered statistically significant.

Results

In total, 24 patients with a ruptured AAA were assessed. Ischaemic colitis was diagnosed in 11 of these patients. A large proportion (seven of 11) of the patients with intestinal complications following aneurysm repair had significant complications from dysfunction of other organ systems, for example acute tubular necrosis or sepsis. Of these patients, six died, one from rebleeding and five from late organ failure with sepsis. The demographic details of the control groups with pneumonia, elective aneurysm repair and sepsis were similar.

Aortic clamping time was longer in the group with a ruptured AAA with ischaemic complications than in the patients who had elective AAA repair and no ischaemic complications ($P<0{\cdot}05$). Also, the three aneurysm subgroups differed with regard to perioperative haemodynamic state (*Table 1*).

Table 1 Comparison of demographic details between patients having acute or elective aneurysm repair

	Ruptured AAA	Ruptured AAA with ischaemia	Elective AAA
No. of patients	13	11	5
Age (years)*	71·2(8·5)	71·1(11·7)	61·6(13·4)
Sex ratio (M:F)	11:2	11:0	5:0
Presurgical shock	5 of 10	8 of 11	0 of 4†
Lowest MAP during surgery (mmHg)*	67·4(42·0)	61·1(13·0)	74·5(19·2)
Duration of shock (min)*	71(58)	82(45)	26(10)†
Blood loss (litres)*	7·4(6·5)‡	5·3(6·4)	1·4(0·9)
Clamping time (min)*	68·9(43·8)	108·9(52·2)§	55·4(33·7)
Survival rate	7 of 13	5 of 11	5 of 5

All groups were comparable with respect to age, sex, the lowest mean arterial pressure (MAP) during surgery and survival. *Values are mean(s.d.). AAA, abdominal aortic aneurysm. †$P<0{\cdot}05$ (elective AAA *versus* ruptured AAA and ruptured AAA with ischaemia); ‡$P<0{\cdot}05$ (ruptured AAA *versus* elective AAA); §$P<0{\cdot}05$ (ruptured AAA with ischaemia *versus* ruptured AAA and elective AAA) (Student *t* test, χ^2 test)

D-lactate and L-lactate levels

The mean time from aortic clamping until blood sampling was 6·3 (range 3–12) h in the ruptured AAA group. The median duration from blood sampling until colonoscopy was 9 (range 2–16) days. Mean(s.d.) D-lactate and L-lactate levels are shown in *Fig. 1*. D-lactate levels were significantly higher in patients after ruptured AAA with colonic ischaemic complications compared with levels in patients with no such complications ($P<0{\cdot}01$) and after elective AAA repair ($P<0{\cdot}01$). Mean D-lactate levels in healthy subjects, patients with pneumonia, and in those with septic shock and acute tubular necrosis were not raised above baseline. No differences in L-lactate level between patients with pneumonia or septic shock and those with or without colonic ischaemia after ruptured AAA repair could be found. L-lactate levels in healthy

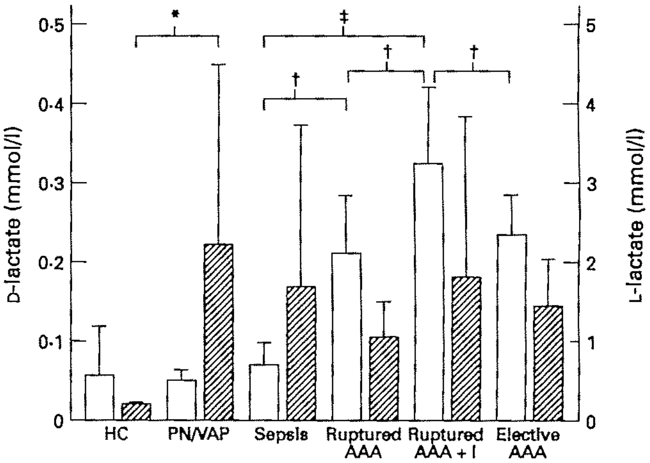

Fig. 1 D-lactate (□) and L-lactate (▨) levels for the different groups. Values are mean(s.d.). HC, healthy controls; PN/VAP, pneumonia or ventilator-associated pneumonia; Sepsis, septic shock and acute tubular necrosis; AAA, abdominal aortic aneurysm; + I, with colonic ischaemia. *$P<0{\cdot}05$, †$P<0{\cdot}01$, ‡$P<0{\cdot}001$ (Student's *t* test)

controls, however, were significantly lower than those in patients with pneumonia and with septic shock and acute tubular necrosis ($P < 0·05$).

If a cut-off point for D-lactate concentration of greater than 0·20 mmol/l is taken in patients with ruptured AAA, then the sensitivity for prediction of ischaemic colitis was 82 per cent (nine of 11) with a specificity of 77 per cent (ten of 13), with negative and positive predictive values of 75 and 83 per cent respectively. One patient had a low D-lactate level (0·16 mmol/l) on admission to the ICU, 3 h after surgery. The next day the level of D-lactate was already 0·45 mmol/l and remained high. On day 10 after surgery, ischaemic colitis grade 3 was diagnosed on endoscopy.

Discussion

This study was undertaken to investigate the value of measuring D- or L-lactate concentration in serum after acute aneurysm repair in prediction of colonic ischaemia. D-lactate is produced by several bacteria commonly found in the gut, such as *Escherichia coli*. It is probably not metabolized by the liver. Serum D-lactate levels in the peripheral blood may closely represent the concentration in the portal vein. In a previous study in rats, Murray *et al.*[21] showed increased levels of D-lactate in peripheral blood samples 2 h after ligation of the superior mesenteric artery. In this study D-lactate concentration was raised at a mean of 6 h after the start of aortic clamping in patients who later (median 9 days) developed ischaemic colitis. The increased D-lactate levels may be due to increased intestinal permeability[22,23]. One of the earliest manifestations of splanchnic ischaemia is an increase in intestinal permeability, during either the hypoperfusion phase or the reperfusion phase of aneurysm repair[24]. Bacterial translocation occurs in both experimental and clinical conditions of intestinal hypoperfusion[22,23], and has been related to the development of postoperative complications and organ failure[25,26].

Another explanation for the increased D-lactate levels may be bacterial overgrowth which can occur for several reasons, such as short bowel syndrome[27,28]. It has been shown that following colonic ischaemia the number of *E. coli* can increase rapidly[29], resulting in increased plasma D-lactate levels[30].

Normal D-lactate levels in patients with septic shock and acute tubular necrosis indicate that a period of complete ischaemia combined with systemic haemodynamic deterioration may be necessary to induce D-lactate release from intestinal bacteria in the early postoperative phase. This may be supported by the finding of increased D-lactate levels in patients with mesenteric occlusion in a study by Murray *et al.*[18]; patients with other causes of acute abdominal pain had normal levels.

In this study the sensitivity and specificity of increased levels of D-lactate in predicting ischaemic complications were 82 and 77 per cent respectively. Murray *et al.*[18] found a sensitivity and a specificity of 90 and 87 per cent respectively for raised D-lactate concentration in patients with mesenteric occlusion. This difference may be due to the retrospective selection of patients in the present study. In patients with colonic ischaemia following ruptured AAA, only those with the most severe colonic ischaemia were included, because colonoscopy was performed only after clinical suspicion. Therefore D-lactate levels in patients without colonic ischaemia may have been higher because those with mild ischaemic changes were also included in this subgroup. Irrespective of this possible bias, D-lactate seems to be a good marker to identify severe colonic ischaemia at an early stage.

The value of L-lactate in the assessment of adequacy of tissue perfusion and oxygenation is limited by several confounding variables, such as liver function, acute changes in acid–base balance, and interorgan exchange of lactate[31]. Despite this, measurement of blood lactate levels provides a marker of metabolism and tissue perfusion[15]. L-lactate levels were increased in patients with a ruptured AAA compared with those in healthy subjects, and tended to be higher in patients with intestinal complications after ruptured AAA repair. However, L-lactate concentration was also higher in patients with pneumonia or septic shock than in healthy subjects, probably indicating the presence of tissue hypoxia in organs other than those of the gastrointestinal tract. L-lactate levels were higher in patients with pneumonia than after elective aneurysm repair. Since L-lactate, when produced in the intestinal tract, can be metabolized rapidly by the liver, this first-pass effect may have resulted in these differences. L-lactate produced in other tissues enters the systemic circulation directly.

The results of this study indicate that D-lactate may be a more specific marker for colonic ischaemia after surgery for a ruptured aortic aneurysm than L-lactate, which has a raised concentration in other critical illnesses. A prospective study is therefore justified to investigate the full value of determining D-lactate levels in patients at risk of colonic ischaemia following repair of a ruptured abdominal aneurysm.

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Predischarge duplex imaging of infrainguinal vein grafts does not predict the development of stenoses

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Background The aim of this study was to determine whether predischarge duplex imaging of an infrainguinal vein graft could predict the subsequent development of graft stenosis.

Methods Patients with infrainguinal vein grafts underwent a duplex scan of the entire graft before discharge from hospital. Grafts were classified as abnormal or normal based on the presence or absence of flow abnormalities (peak velocity ratio 1·5 or greater). All grafts were re-examined 1 month after surgery, at 3-monthly intervals for the first year and then every 6 months thereafter. A significant stenosis requiring correction was defined by a duplex-derived peak systolic velocity ratio of 3·0 or more. The relationship between the predischarge scan and subsequent development of stenosis was examined.

Results Forty-four grafts were recruited. Two occluded soon after a normal predischarge scan and were excluded from subsequent analysis. Predischarge abnormalities were found in 16 grafts. The abnormality in one graft required immediate correction. A further four grafts subsequently developed significant stenoses and required angioplasty. Of the 26 grafts with no predischarge abnormalities, 11 developed significant stenoses and underwent angioplasty. Abnormal predischarge duplex scans had a sensitivity and specificity of 31 and 58 per cent respectively for the development of stenoses. The positive and negative predictive values were 31 and 58 per cent respectively.

Conclusion Predischarge duplex imaging cannot be used to predict the development of stenoses in infrainguinal vein grafts.

Although infrainguinal vein graft surveillance programmes have been instituted by many vascular units[1–4], their implementation increases workload and costs[5]. In theory, not all vein grafts require surveillance as only a proportion will develop stenoses. The early identification of high-risk grafts could allow selective and hence more cost effective surveillance. Recent reports suggest that the development of vein graft stenosis is preceded by flow abnormalities that can be detected soon after operation[6,7]. Wilson and colleagues[7] have recommended predischarge duplex imaging for the early detection of intrinsic abnormalities that may develop into significant stenoses. Similarly, Mills *et al.*[6] suggested that grafts with a normal duplex scan after the first 3 months of surveillance require less intensive follow-up. The purpose of this study was to determine whether duplex imaging of infrainguinal vein grafts before hospital discharge and after 3 months can indeed detect abnormalities that will develop into significant stenoses.

Patients and methods

A prospective study was undertaken of consecutive infrainguinal vein grafts performed between August 1995 and April 1997. All patients who had infrainguinal vein bypass underwent colour duplex imaging before discharge from hospital. Scans were usually done at least a week after surgery. The dressings were taken down and the wounds covered with Opsite dressing (Smith and Nephew, Hull, UK). The patients were examined supine. In all cases the probe was covered with a probe cover and sterile gel was applied to the surface of the Opsite. Scans were performed by an experienced vascular technologist using one of two colour duplex scanners (Diasonics Masters, Diasonics Sonotron, Bedford, UK or ATL Ultra mark 9 HDI, ATL, Letchworth, UK). Handheld probes of either 5 or 10 MHz were used.

The site and nature of all flow abnormalities (defined as a peak velocity ratio (PVR) of 1·5 or more, or an area of turbulent blood flow) detected at this first scan were noted. The PVR[8] was calculated as the ratio of the peak systolic velocity within the stenosis and the peak systolic velocity in an adjacent segment of normal graft.

Following discharge from hospital, patients were entered into a postoperative surveillance programme. This entailed imaging 1 month after surgery, at the end of the third month then every 3 months for the first year and 6 monthly thereafter. At each visit, the whole graft was imaged and any changes in previously noted lesions were recorded. It is the policy of the unit to correct by angioplasty any stenosis which has a PVR of 3·0 or above.

To determine the predictive value of predischarge imaging, the natural history of grafts with normal and abnormal predischarge scans was analysed at the end of the study. Similarly the ability of duplex imaging performed at 3 months to predict subsequent graft stenosis was analysed.

Results

Forty-four grafts were performed in 43 patients. There were 21 *in situ* vein grafts, 17 reversed grafts and six composite arm–saphenous vein grafts. Two *in situ* grafts occluded soon after the predischarge scan and are not included in the data analysis. One of these occluded because of run-off disease and the other had required thrombectomy within 48 h of surgery. Both had normal scans before discharge. The remaining 42 grafts each had at least two postoperative surveillance scans. The median (range) follow-up time for patent grafts was 20 (9–29) months. Three deaths occurred during the study and one patient was lost to follow-up.

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Predictive value of the predischarge scan

Sixteen grafts were classified as abnormal based on the detection of lesions on the predischarge scan. These predischarge abnormalities consisted of stenosis with a PVR of 1·5–3·0 in 13 grafts and areas of flow disturbance in three grafts. One of these grafts had a lesion with an initial PVR of 3·0 that required immediate correction by angioplasty. Four other abnormal grafts subsequently developed significant stenoses at a median (range) time of 4 (4–6) weeks after surgery. These stenoses had a median (range) PVR of 3·0 (3·0–5·0) and were all located at the site of the original abnormalities. Lesions that regressed either had no residual flow abnormality ($n = 9$) or a persistent PVR of less than 2·0 ($n = 2$).

Of the 26 'normal' grafts, 11 developed significant abnormalities during postdischarge surveillance. These occurred at a median (range) of 15 (5–85) weeks after surgery and consisted of stenoses with PVRs of between 3·5 and 7·0. The outcome of the grafts is summarized in *Fig. 1*. The sensitivity and specificity of predischarge abnormalities in predicting the development of future graft stenoses were 31 and 58 per cent respectively. The positive and negative predictive values were 31 and 58 per cent respectively.

Predictive value of the 3-month duplex scan

At the end of 3 months, 31 of the original 42 grafts remained patent and had not required angioplasty (*Fig. 2*). The 3-month duplex scan detected flow abnormalities with PVRs of between 1·5 and 2·5 in six of these grafts, two of which then developed stenoses with PVRs of 4·0 and 7·0. The flow abnormalities in the other four abnormal grafts resolved completely.

The 3-month duplex scan found no flow abnormalities in 25 of the 31 grafts. Three of these normal grafts subsequently developed significant stenoses at 4, 5 and 28 months after operation, and underwent angioplasty. The sensitivity and specificity of the 3-month duplex scan in predicting future graft stenoses were 40 and 85 per cent respectively. The positive and negative predictive values were 33 and 88 per cent respectively.

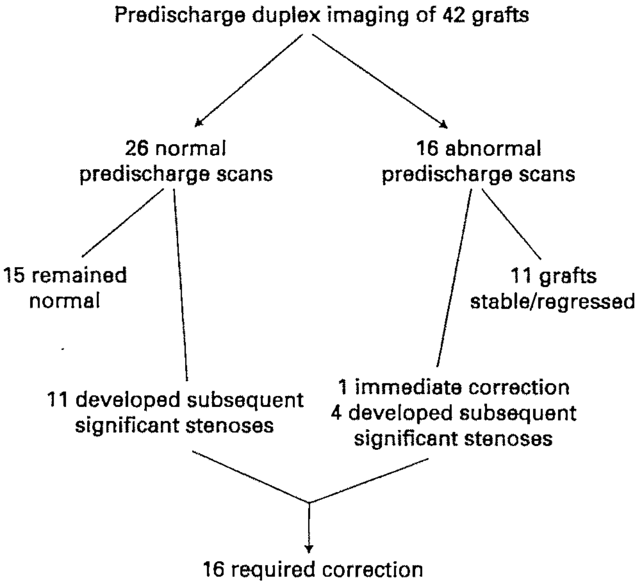
Predischarge duplex imaging of 42 grafts
26 normal predischarge scans
16 abnormal predischarge scans
15 remained normal
11 grafts stable/regressed
11 developed subsequent significant stenoses
1 immediate correction
4 developed subsequent significant stenoses
16 required correction

Fig. 1 Outcome of grafts following predischarge duplex imaging

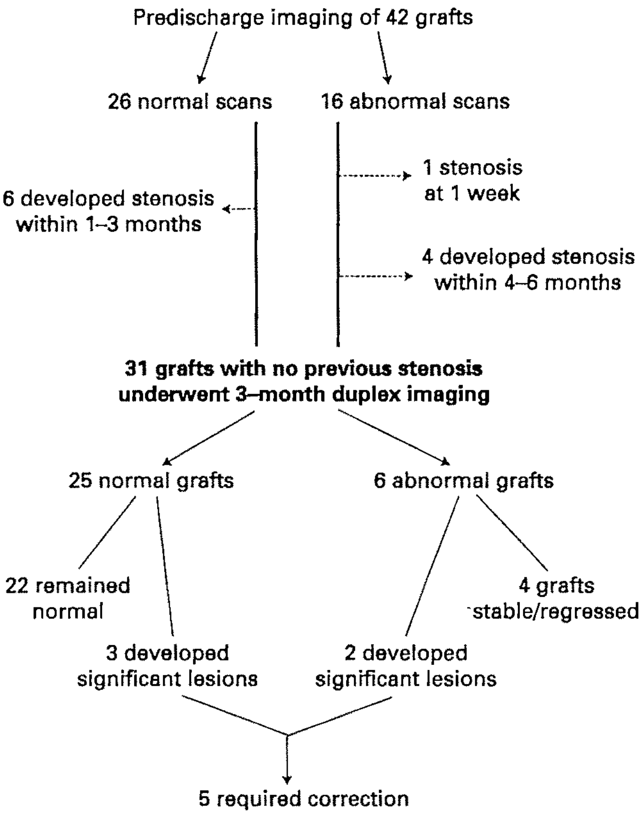
Predischarge imaging of 42 grafts
26 normal scans
16 abnormal scans
1 stenosis at 1 week
6 developed stenosis within 1–3 months
4 developed stenosis within 4–6 months
31 grafts with no previous stenosis underwent 3–month duplex imaging
25 normal grafts
6 abnormal grafts
22 remained normal
4 grafts stable/regressed
3 developed significant lesions
2 developed significant lesions
5 required correction

Fig. 2 Outcome of grafts following duplex imaging at 3 months

Discussion

Although duplex-based graft surveillance is widely practised, it is still very much in an evolutionary phase and is controversial. Some authors highlight the limitations and doubt the cost effectiveness of surveillance[9,10] while others have examined ways of improving its practice[11–14]. Recent studies have suggested that stenoses develop from intrinsic graft abnormalities and that such abnormalities can be detected within the first few weeks after operation[6,7]. This study examined the value of predischarge duplex imaging. Only five of the 16 grafts with predischarge abnormalities developed stenoses, whereas 11 of the 26 grafts that were normal at discharge subsequently developed a stenosis. From these data it is clear that, although predischarge scans can identify early abnormalities, these abnormalities are of low predictive value for the development of significant stenoses. In agreement, Passman *et al.*[14] found that only 14 per cent of grafts that eventually developed significant stenoses could be identified by duplex imaging within 2 weeks of surgery.

Wilson *et al.*[7] recently published their experience with predischarge imaging. They found that 30 per cent of grafts with abnormal predischarge scans developed stenoses. However, data on the outcome of grafts with normal predischarge scans were not presented and the overall value of predischarge imaging in their graft surveillance practice was therefore not clear. In a study of

135 infrainguinal vein grafts, Mills *et al.*[6] used the outcome of serial duplex imaging performed during the first 3 months after operation to predict which grafts would develop a stenosis. Of 44 grafts that had flow abnormalities at 3 months, 20 subsequently developed stenoses. Conversely, of the remaining 91 grafts that were normal at 3 months, only two required revision. This outcome is not surprising because it is known that more than 60 per cent of graft stenoses develop within 3 months of surgery[15]. Thus a 3-month scan is not truly being used to 'predict' stenosis development because the majority of stenoses have already developed by this time. For comparative purposes, analysis of data in this study using similar criteria found that 11 of the 16 significant stenoses had developed within the first 3 months. However, even though the 3-month duplex scan had a better predictive value than the predischarge scan it had a low sensitivity. In the first year of routine surveillance in the present study, 210 postdischarge scans were performed in 42 grafts. If after 3 months of surveillance only the 11 previously stenosed grafts and the six grafts which had flow abnormalities at 3 months were still scanned, as recommended by Mills and colleagues[6], then 135 scans would have been performed in the year. This policy would have saved the cost of 75 scans but would have missed stenoses in three grafts.

To date, there is no method of limiting the number of grafts undergoing postoperative surveillance. A better understanding of the natural history of graft stenoses is needed. The findings of the present study imply that vein graft stenoses do not develop from intrinsic areas of abnormality as previously suggested. Grafts that develop a stenosis in the long term cannot easily be predicted. Predischarge duplex imaging cannot be used to allocate grafts into high- and low-risk categories for the purposes of future surveillance.

Acknowledgements

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In vivo pressure profiles of thigh-length graduated compression stockings

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Background The aim of the study was to assess whether the appropriate pressure profile is generated by thigh-length graduated compression stockings in human subjects. The effect of leg posture on the pressure profile was assessed in three commonly used brands of graduated compression stockings.

Methods The study involved 17 human volunteers from the Department of Orthopaedic Surgery. Three different brands of stockings commonly recommended for the prevention of deep vein thrombosis were applied to each individual and the interface pressure profile under the stocking was measured. The effect of posture was assessed by comparing the interface pressure profile with the subject supine and in standing and sitting positions.

Results Appropriate median pressure profiles were achieved only with the subject standing or supine. In the sitting position with the knee flexed, a high median interface pressure in excess of 28 mmHg was generated at the popliteal fossa. Overall, inconsistent performance was found in all three brands of stockings; fewer than 30 per cent of the pressure readings fell within 20 per cent of the 'ideal'. Reversed pressure profile was observed in over 70 per cent of subjects.

Conclusion Thigh-length graduated compression stockings may be most effective in bedridden patients. Knee-length stockings may be more suitable for the prevention of deep vein thrombosis in ambulant patients.

The scientific basis on which graduated compression stockings were developed originated from the work of Sigel *et al.*[1] and later Lawrence and Kakkar[2]. They studied the effect of graduated compression on femoral venous flow rate in human subjects lying in the supine position, both horizontally and with a 15° tilt. They concluded that an optimal pressure gradient of 18 mmHg at the ankle, 14 mmHg at the calf, 8 mmHg at the knee, 10 mmHg at the lower thigh and 8 mmHg at the upper thigh would generate the fastest venous flow. Commercial graduated compression stockings have since been manufactured to produce such a pressure profile. Quality control of the garment is governed by the British Standard (BS6612: 1985). It is based on the Hosiery Trade Research Association (HATRA) system, a mechanical testing model, to measure the pressure profile of stockings. Thomas[3] tested ten brands of graduated compression stockings using the HATRA model and found that they generated very different pressure profiles; some even generated an adverse 'reversed' gradient.

Measurement of *in vivo* pressure profiles on human subjects is difficult and published data are scarce[4,5]. Furthermore, the effect of posture has not been studied. Since patients spend the majority of their daytime convalescence after operation sitting in a chair, it is important to examine the effect of body posture on the pressure profile of graduated compression stockings.

Methods

Thigh-length graduated compression stockings were tested for their compression pressure profiles in 17 healthy volunteers (nine men and eight women). The three most commonly used stockings were tested: TED (Kendall, Basingstoke, UK), Tx (Brevet, Seton Health Group, Oldham, UK) and Anti-Em (Biersdorf UK, Milton Keynes, UK).

The Oxford interface pressure monitor MkII (Talley, Romsey, UK) was used to record the pressure under the stockings. The range of this pressure monitor was 0–300 mmHg and its accuracy was ± 4 mmHg. The pressure monitor utilizes 2-cm^3 air cells to detect the interface pressure. These air cells were placed on standard positions along the leg: (1) 2 cm above and anterior to the tip of the medial malleollus; (2) midway between the tip of the medial malleolus and the medial femoral condyle; (3) 5 cm above the midpoint of the upper border of the patella; (4) 1 cm above the popliteal skin crease; (5) two-thirds of the way down a line joining the anterior superior iliac spine and the midpoint of the superior border of the patella; and (6) underneath the elastic band of the stocking.

The positions on the leg were marked carefully and the stocking applied over the air cells taking care to avoid kinking of the tubing or the sensors. The pressures generated by the stocking were recorded. Three sets of recordings were taken and the median values were used for analysis.

Pressure readings were taken in four different body positions: (i) supine, (ii) standing, (iii) sitting with the knee flexed to 90° and (iv) sitting with the knee flexed to 45°. The same process was repeated with each brand of stockings. Each volunteer had both legs tested.

To verify the repeatability of the method of testing, the three investigators performed a preliminary study by testing one brand of stockings on one another on three separate occasions. The mean(s.e.m.) intraobserver error was 0·3(3·3) mmHg. The mean(s.e.m.) interobserver error was 0·8(2·5) mmHg.

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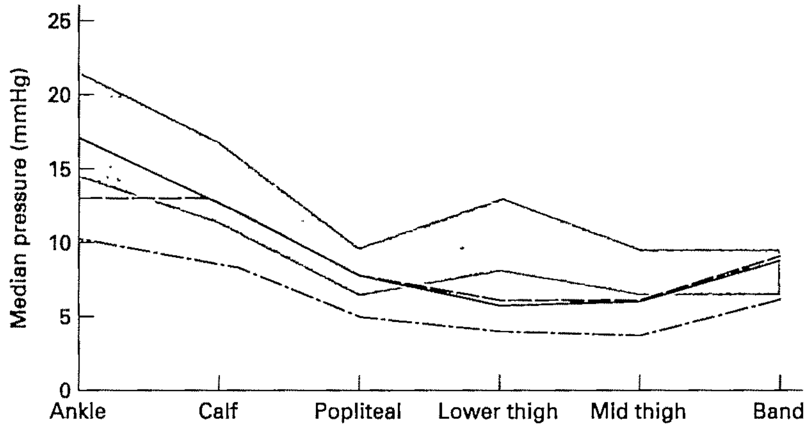
Results

Seventeen subjects were tested; both legs were examined using three different brands of stockings in four body positions. A total of 408 sets of pressure profiles were obtained. *Figs 1–4* illustrate the median pressure profiles of the three brands of stockings in four body positions. The shaded areas on these graphs represent the ± 20 per cent limits of the 'ideal' pressure profile as recommended by Sigel *et al.*[1] and Lawrence and Kakkar[2]. All three types of stockings generated very variable pressures in all positions along the leg, particularly at the ankle and popliteal fossa.

The stockings performed best with the subject in the standing position; the median pressures fell within the ideal band from the knee down and also showed good graduated compression. The most significant result, however, was the very high peak popliteal fossa pressure when the subjects were tested in a sitting position with their knees flexed to 90°. In one subject, the highest popliteal pressure recorded was 310 mmHg. These high popliteal pressures would reverse the pressure gradient and could cause venous or even arterial obstruction.

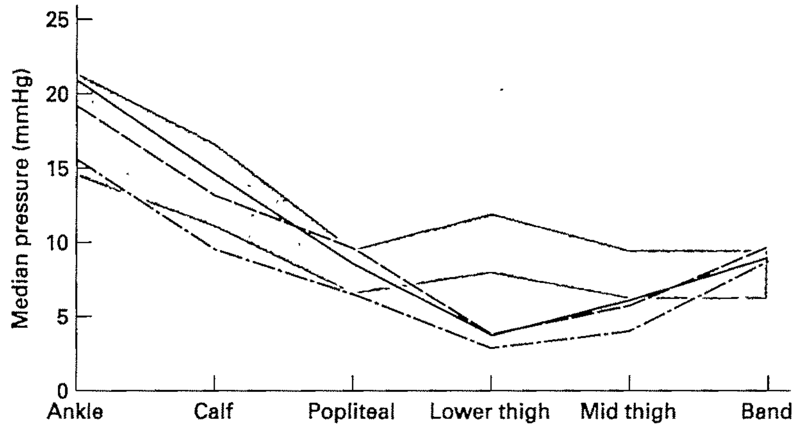
There was a wide variation in the pressures generated by the stockings. The proportion of readings that fell within the ideal range for each stocking was as follows:



Pressure (mmHg)

Biersdorf	17 (10·3–20·7)	12·7 (5·7–19)	7·7 (2·3–12·3)	5·7 (3·3–8)	6 (5–8)	8·7 (7–9·7)
Kendall	10·3 (6–16·7)	8·7 (5–12)	5 (1·3–9·7)	4 (2–6·3)	3·7 (2–5)	6 (5–8)
Brevet	13 (8·3–18)	12·7 (10·3–16·7)	7·7 (4·7–10)	6 (4·3–7·3)	6 (4–7·7)	9 (8–12)

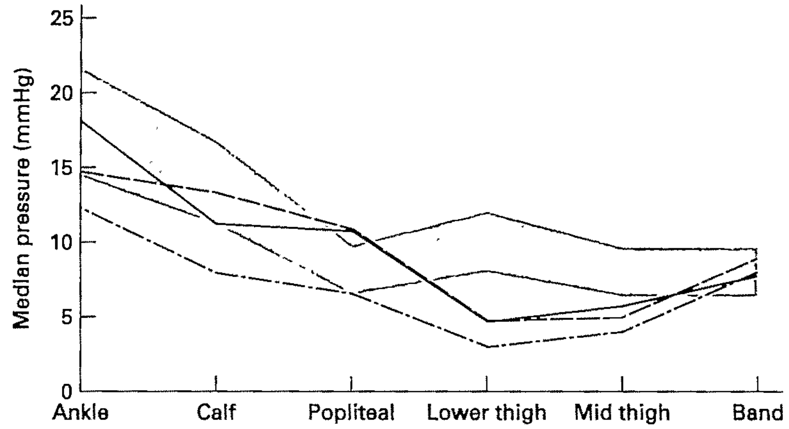
Fig. 1 Median pressure profile in the supine position for Biersdorf (———), Kendall (—·—·) and Brevet (— — —) stockings. The shaded area represents the ± 20 per cent ideal. Values in the panel below are median (interquartile range)



Pressure (mmHg)

Biersdorf	21 (14·7–26·3)	14·7 (10–19·3)	8·7 (3·3–14)	4 (2–7·3)	6 (3–7·3)	9 (5·7–11·7)
Kendall	15·7 (9·7–23)	9·7 (6·3–13·3)	6·7 (2–12)	3 (1–5·3)	4 (2·3–5·3)	8·7 (6–11)
Brevet	19·3 (11·3–26)	13·3 (11·3–18·7)	9·7 (6–12·7)	4 (2·7–6)	5·7 (5·3–6·7)	9·7 (7–12·3)

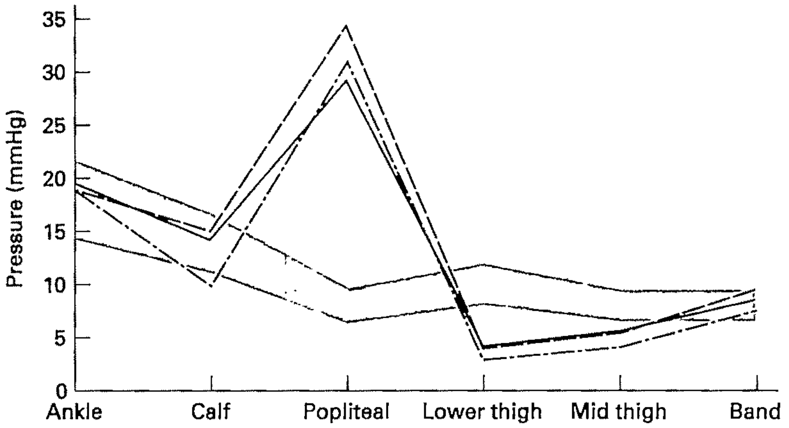
Fig. 2 Median pressure profile in the standing position for Biersdorf (———), Kendall (—·—·) and Brevet (— — —) stockings. The shaded area represents the ± 20 per cent ideal. Values in the panel below are median (interquartile range)



Pressure (mmHg)

Biersdorf	18 (13–22·3)	11·3 (8–15·3)	10·7 (7·3–16)	4·3 (1·7–8·3)	5·7 (4–7·3)	7·7 (6·7–9·7)
Kendall	12·3 (5·3–19·3)	8 (5·3–11·3)	6·7 (3·3–19·7)	3 (2–6)	4 (2–5·3)	8 (5–13)
Brevet	14·7 (11·3–21·3)	13·3 (10–16·3)	11 (6·3–25·3)	4·7 (4–7)	5 (4–6·7)	9 (7·7–11)

Fig. 3 Median pressure profile in the sitting position with the knee flexed to 45° for Biersdorf (———), Kendall (—·—·) and Brevet (— — —) stockings. The shaded area represents the ± 20 per cent ideal. Values in the panel below are median (interquartile range)



Pressure (mmHg)

Biersdorf	19·3 (14–28·3)	14·3 (9–21)	28·7 (17–89)	4·3 (1·7–8·3)	5·7 (4–7·3)	8·3 (6·7–10·7)
Kendall	19 (10·7–25·3)	10 (6–14·3)	30·3 (8–80·3)	3 (2–6)	4 (2.3–6·3)	7·3 (5·3–12·7)
Brevet	18·7 (12–30·7)	15 (10–18·3)	33·7 (15–100)	4 (3·3–7)	5·3 (4·7–7)	9·3 (8–12·3)

Fig. 4 Median pressure profile in the sitting position with the knee flexed to 90° for Biersdorf (———), Kendall (—·—·) and Brevet (— — —) stockings. The shaded area represents the ± 20 per cent ideal. Values in the panel below are median (interquartile range)

Biersdorf 27·6 per cent, Brevet 26·9 per cent and Kendall 20·0 per cent. The difference between the Kendall stocking and the other two brands was statistically significant ($P = 0{\cdot}01$, χ^2 test). There was no significant difference between the brands of stockings in the number of legs that showed a reversed pressure gradient.

Discussion

The assessment of *in vivo* pressure profiles in thigh-length graduated compression stockings is difficult. Air- and fluid-filled devices are not suitable because they cause localized ballooning, raising the pressure spuriously. The Oxford pressure monitor uses empty air cells which do not distort the contour of the fabric. The interface pressure is measured as air is pumped into these cells. Only 2 cm^3 of air is used which causes negligible ballooning.

Another factor that causes difficulty in this type of measurement is that the human leg does not conform to any uniform geometrical shape. The tension and pressure generated by the stockings are therefore not uniformly distributed. By standardizing the positions of the air cells with reference to definite surface anatomical landmarks, the variability in measurement was minimized. The preliminary reproducibility study showed that a mean(s.e.m.) intraobserver error of 0·3(3·3) mmHg and mean(s.e.m.) interobserver error of 0·8(2·5) mmHg could be achieved; previous studies did not validate their methods[4,5].

This study showed that all three brands of thigh-length graduated compression stocking performed poorly *in vivo*. The ideal pressure profile of 18, 14, 8, 10 and 8 mmHg from ankle to thigh was rarely reproduced and in over 75 per cent of cases the pressure gradient was reversed. There was little to choose between the brands but Kendall stockings produced a lower pressure profile, often falling below the ± 20 per cent ideal range.

Body position also has an important effect on the interface pressure. Around the ankle and the knee, the pressure was often drastically raised as the joint was flexed. As the ankle or the knee joint flexes, the cross-sectional circumference increases causing the tension in the fabric to rise. The manufacturers have incorporated a heel patch with a different weave to provide a more elastic 'give'; however, no such weave is present at the knee. It was no surprise that the interface pressure was markedly raised when the joint was flexed to 90°. A median pressure of over 28 mmHg was recorded at the popliteal fossa in this position and such high pressure would 'reverse' the pressure gradient causing distal venous stagnation.

Graduated compression stockings are effective in reducing the rate of postoperative deep vein thrombosis in abdominal and orthopaedic surgery[6–17]. In a randomized controlled trial in patients undergoing joint replacement carried out in the authors' own centre[18], thigh-length stockings did not produce any significant reduction in deep vein thrombosis. The findings from the present study also cast doubt on the effectiveness of thigh-length graduated compression stockings. Thigh-length stockings generated satisfactory pressure profiles when the leg was straight and could be most effective in bedridden patients. However, patients spend long intervals sitting in a chair after joint replacement operations. The high popliteal pressure generated by the stockings in this position may explain why they failed to prevent deep vein thrombosis. Knee-length stockings are cheaper and may be as effective in preventing postoperative deep vein thrombosis[19,20].

Acknowledgements

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Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomized controlled trials

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Background A systematic review was carried out to assess the relative efficacy of antimicrobial prophylaxis for the prevention of postoperative wound infection in patients undergoing colorectal surgery.

Methods MEDLINE, EMBASE, the Cochrane Trials Register and the references cited in retrieved studies were searched to identify relevant trials published between 1984 and 1995.

Results Some 147 relevant trials were identified. The quality of trials has improved over the past 12 years. The results confirm that the use of antimicrobial prophylaxis is effective for the prevention of surgical wound infection after colorectal surgery. There was no significant difference in the rate of surgical wound infections between many different regimens. However, certain regimens appear to be inadequate (e.g. metronidazole alone, doxycycline alone, piperacillin alone, oral neomycin plus erythromycin on the day before operation). A single dose administered immediately before the operation (or short-term use) is as effective as long-term postoperative antimicrobial prophylaxis (odds ratio 1·17 (95 per cent confidence interval (c.i.) 0·90–1·53)). There is no convincing evidence to suggest that the new-generation cephalosporins are more effective than first-generation cephalosporins (odds ratio 1·07 (95 per cent c.i. 0·54–2·12)).

Conclusion Antibiotics selected for prophylaxis in colorectal surgery should be active against both aerobic and anaerobic bacteria. Administration should be timed to make sure that the tissue concentration of antibiotics around the wound area is sufficiently high when bacterial contamination occurs. Guidelines should be developed locally in order to achieve a more cost-effective use of antimicrobial prophylaxis in colorectal surgery.

It is generally accepted that antimicrobial prophylaxis is one of many measures that should be taken to prevent postoperative wound infection in contaminated or clean-contaminated surgery[1]. Many different antimicrobials are available with different pharmacokinetic and pharmacodynamic features, spectrums of activity and toxicity. To achieve the most cost-effective use of antimicrobial prophylaxis, decisions need to be made about the choice, regimen and delivery of antimicrobial agents[2–5].

Because of a high risk of endogenous contamination by bacteria in the contents of the large bowel, colorectal surgery is associated with a high risk of surgical wound infection. This review aims to evaluate the relative efficacy of antimicrobial prophylaxis in patients undergoing colorectal surgery, focusing on the choice of antibiotics, timing and duration of administration.

Methods

The review includes randomized controlled trials, published between 1984 and 1995, that evaluated antimicrobial prophylaxis for preventing surgical wound infection after colorectal surgery. A search of MEDLINE (1984–1995), EMBASE/EMBASE Alert (1983–1995) and the Cochrane Trials Register was conducted with the assistance of the information services at the NHS Centre for Reviews and Dissemination. The titles and abstracts of 'hits' were assessed and copies of potentially relevant studies were acquired. The references cited in retrieved trials and review articles were checked to locate other relevant trials. A selection of key journals (*British Journal of Surgery*, *Journal of Antimicrobial Chemotherapy*, *Archives of Surgery*, *Annals of Surgery* and *Acta Chirurgica Scandinavica*) was also searched. Studies in all languages were considered. More details of search strategies used are available elsewhere[6].

When different regimens of antibiotic prophylaxis are compared, the mortality rate becomes very low in all groups[7]. In this review, the rate of surgical wound infection was used as the principal outcome measure to assess the relative efficacy of antimicrobial prophylaxis in colorectal surgery. The definition and diagnosis of surgical wound infection often varies in published studies. Where possible, only abdominal wound infections were included because of their reliability. However, in some trials it was not clear whether perineal wound infections or other infections related to the surgical procedures were also included; in these cases, the reported results were used.

The relevance and validity of each study was assessed and data were extracted by one reviewer and checked by another. Study quality was assessed by noting method of randomization, blind outcome assessment, written definition of surgical wound infection, withdrawals and an *a priori* calculation of sample size. To give a visual summary of each study result, the odds ratios and their 95 per cent confidence intervals were presented in diagrams. Where appropriate (e.g. when the same regimen of antibiotic prophylaxis was assessed in several trials), formal meta-analysis was carried out using the Mantel–Haenszel method (in Cochrane Review Manager Software, version 3.0 for Windows, Cochrane Collaboration, Oxford, UK) to calculate the overall or pooled odds ratio and χ^2 method to test heterogeneity. A fixed-effects model was used unless statistically significant heterogeneity was found among trial results at the 10 per cent level of significance[8].

A total of 147 trials (published in 144 papers) met the inclusion criteria. The majority of these studies ($n = 129$) were identified through a search of MEDLINE databases. Nine studies were located by searching EMBASE, three studies by cross-checking citations in identified articles and three more from the Cochrane Trials Register. No additional trials were located during the handsearch of key journals. Of trials included,

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134 were published in English and 13 in other languages. These trials were conducted in 25 different countries; a quarter in the UK.

More than 70 different antibiotics or combinations of antibiotics have been assessed in the included trials (without considering different doses or duration of the same antibiotics or antibiotic combinations). There is insufficient space in this paper to discuss all prophylactic regimens included, although details of all trials are available elsewhere[6]. Only the results of trials that evaluated cefuroxime plus metronidazole and gentamicin plus metronidazole are presented specifically because these regimens are recommended in *The British National Formulary*[9]. This paper focuses on the evidence for newer-generation cephalosporins, combinations of antibiotics and single *versus* multiple doses. The route of administration, adverse effects and cost effectiveness are also considered.

Results

The quality of the included trials has improved over the past 12 years. The proportion of trials in which randomization was reported to be concealed until the point of patient allocation was 30, 33 and 65 per cent respectively for three time periods 1984–1987, 1988–1991 and 1992–1995. More multicentre studies have been published recently, and the overall sample size was smaller than 100 in 56 per cent of the trials published during 1984–1987, 34 per cent during 1988–1991 and in only one of the 23 trials published since 1992. Trials published between 1992 and 1995 were also of better quality in terms of prior calculation of sample size, defining surgical wound infection, adequate follow-up and reporting of withdrawals. However, the proportion of trials with blind outcome assessment has not changed: 44, 34 and 44 per cent respectively for the three time periods 1984–1987, 1988–1991 and 1992–1995. Few trials compared the same regimens and so it was not possible to assess generally how trial quality affects study results.

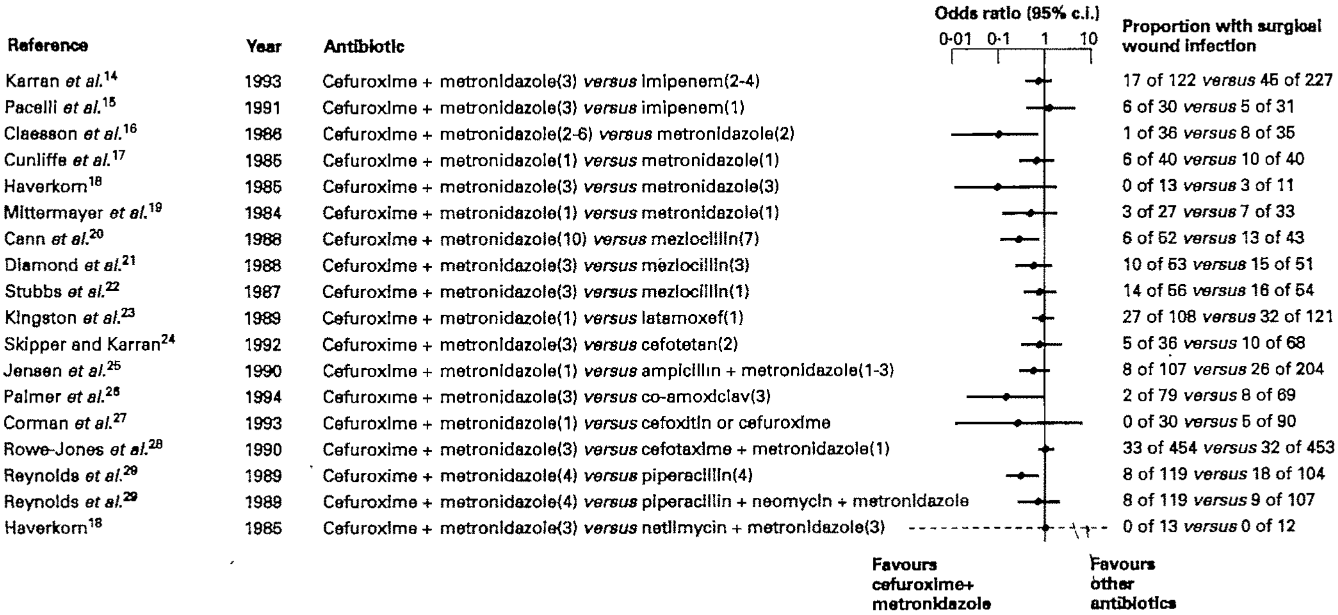
The criteria for inclusion and exclusion were described in 87 per cent of the included trials. The frequently stated criteria for exclusion were allergy to study drugs, preoperative use of other antibiotics, impaired renal or liver function, young or extreme age, pregnancy or lactation, and certain types of colorectal operations.

The review identified four trials published since 1984 that compared patients given antibiotic prophylaxis with a control group treated without antibiotics[10–13]. The results from these four trials consistently showed that the surgical wound infection rate was much higher in the control groups than in the antibiotic groups (overall 40 *versus* 13 per cent; odds ratio (OR) 4·08 (95 per cent confidence interval (c.i.) 2·33–7·13)).

Cefuroxime plus metronidazole

Cefuroxime plus metronidazole was tested in 18 comparisons reported in 16 papers (*Fig. 1*)[14–29]. By pooling the results from four trials[16–19], it was found that cefuroxime plus metronidazole was more effective than metronidazole alone (overall OR 0·32 (95 per cent c.i. 0·15–0·68); heterogeneity test, $P = 0{\cdot}41$). Pooling of three trials[20–22] showed that the rate of surgical wound infection was lower in the cefuroxime plus metronidazole group than in the mezlocillin group (overall OR 0·55 (95 per cent c.i. 0·32–0·93); heterogeneity test, $P = 0{\cdot}38$). The rate of surgical wound infection was lower in the cefuroxime plus metronidazole group than that in the piperacillin alone group[29]. Cefuroxime plus metronidazole was more effective than co-amoxiclav in a trial in which there were more reoperations for postoperative complications (such as anastomotic leak or haematoma) in the co-amoxiclav group[26].

The results with cefuroxime plus metronidazole were not significantly different from those with imipenem[14,15], netilmicin plus metronidazole[18], latamoxef[23], cefotetan[24],



Reference	Year	Antibiotic	Proportion with surgical wound infection
Karran *et al.*[14]	1993	Cefuroxime + metronidazole(3) *versus* imipenem(2-4)	17 of 122 *versus* 45 of 227
Pacelli *et al.*[15]	1991	Cefuroxime + metronidazole(3) *versus* imipenem(1)	6 of 30 *versus* 5 of 31
Claesson *et al.*[16]	1986	Cefuroxime + metronidazole(2-6) *versus* metronidazole(2)	1 of 36 *versus* 8 of 35
Cunliffe *et al.*[17]	1985	Cefuroxime + metronidazole(1) *versus* metronidazole(1)	6 of 40 *versus* 10 of 40
Haverkorn[18]	1985	Cefuroxime + metronidazole(3) *versus* metronidazole(3)	0 of 13 *versus* 3 of 11
Mittermayer *et al.*[19]	1984	Cefuroxime + metronidazole(1) *versus* metronidazole(1)	3 of 27 *versus* 7 of 33
Cann *et al.*[20]	1988	Cefuroxime + metronidazole(10) *versus* mezlocillin(7)	6 of 52 *versus* 13 of 43
Diamond *et al.*[21]	1988	Cefuroxime + metronidazole(3) *versus* mezlocillin(3)	10 of 53 *versus* 15 of 51
Stubbs *et al.*[22]	1987	Cefuroxime + metronidazole(3) *versus* mezlocillin(1)	14 of 56 *versus* 16 of 54
Kingston *et al.*[23]	1989	Cefuroxime + metronidazole(1) *versus* latamoxef(1)	27 of 108 *versus* 32 of 121
Skipper and Karran[24]	1992	Cefuroxime + metronidazole(3) *versus* cefotetan(2)	5 of 36 *versus* 10 of 68
Jensen *et al.*[25]	1990	Cefuroxime + metronidazole(1) *versus* ampicillin + metronidazole(1-3)	8 of 107 *versus* 26 of 204
Palmer *et al.*[26]	1994	Cefuroxime + metronidazole(3) *versus* co-amoxiclav(3)	2 of 79 *versus* 8 of 69
Corman *et al.*[27]	1993	Cefuroxime + metronidazole(1) *versus* cefoxitin or cefuroxime	0 of 30 *versus* 5 of 90
Rowe-Jones *et al.*[28]	1990	Cefuroxime + metronidazole(3) *versus* cefotaxime + metronidazole(1)	33 of 454 *versus* 32 of 453
Reynolds *et al.*[29]	1989	Cefuroxime + metronidazole(4) *versus* piperacillin(4)	8 of 119 *versus* 18 of 104
Reynolds *et al.*[29]	1989	Cefuroxime + metronidazole(4) *versus* piperacillin + neomycin + metronidazole	8 of 119 *versus* 9 of 107
Haverkorn[18]	1985	Cefuroxime + metronidazole(3) *versus* netilmycin + metronidazole(3)	0 of 13 *versus* 0 of 12

Fig. 1 Cefuroxime plus metronidazole *versus* other antibiotics in preventing surgical wound infection in colorectal surgery. Values in parentheses are number of doses. c.i., Confidence interval. Dotted line indicates that the odds ratio was not estimable because of zero events in both groups

ampicillin plus metronidazole[25], cefoxitin[27] and cefotaxime plus metronidazole[28].

Gentamicin plus metronidazole

Gentamicin plus metronidazole was tested in 12 trials (*Fig. 2*)[30–41]. It was as efficacious as ampicillin/sulbactam[30], latamoxef[35], cefotetan[37], metronidazole[38], gentamicin plus clindamycin[40] and co-amoxiclav[31]. The rate of surgical wound infection in the gentamicin plus metronidazole group was significantly higher than that in the oral ciprofloxacin plus intravenous metronidazole group[34], and that in the ceftriaxone plus metronidazole group[36].

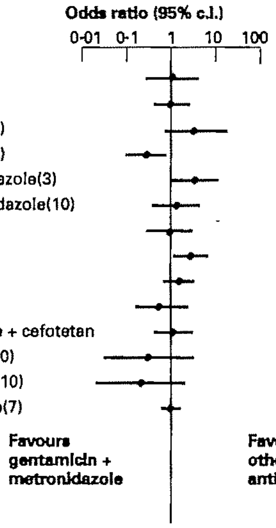
Lau *et al.*[33] found that a single dose of gentamicin plus metronidazole was significantly more effective than oral neomycin plus erythromycin. In another trial, however, Figueras-Felip *et al.*[32] found that gentamicin plus metronidazole (three doses) was associated with a higher rate of surgical wound infection than oral neomycin plus erythromycin, although the difference was not statistically significant (seven of 48 *versus* two of 45; $P = 0{\cdot}16$). The results of the former trial are more reliable because of better study quality in terms of blind outcome measurement, longer follow-up, low drop-out rate and appropriate definition of surgical wound infection. In addition, the timing of antibiotic administration was not optimal in the trial of Figueras-Felip *et al.*; the first dose of gentamicin plus metronidazole was administered 2 h before surgery.

New-generation cephalosporins

Six trials compared a first-generation cephalosporin with a second- or third-generation cephalosporin (*Fig. 3*)[42–46]. The differences in surgical wound infection between groups were not statistically significant in individual trials or after pooling results from all six trials (overall OR 1·07 (95 per cent c.i. 0·54–2·12); heterogeneity test, $P = 0{\cdot}48$).

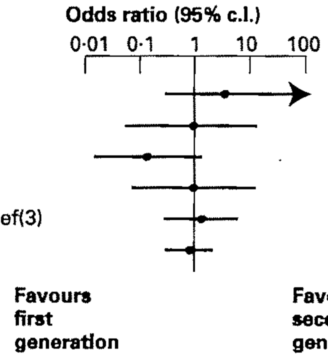
Combinations of antibiotics

Many trials tested whether antibiotics were more effective when used in combination than when used alone (*Fig. 4*)[10,16–19,27,29,33,38,39,46–67]. The overall results from nine trials showed that metronidazole alone was less efficacious than a combination of metronidazole with other antibiotics (17 *versus* 6 per cent; random effects overall OR 3·19 (95



Reference	Year	Antibiotic	Proportion with surgical wound infection
AhChong *et al.*[30]	1994	Gentamicin + metronidazole(3) *versus* ampicillin + sulbactam(3)	7 of 65 *versus* 6 of 63
Hall *et al.*[31]	1989	Gentamicin + metronidazole(2) *versus* co-amoxiclav(2)	18 of 121 *versus* 16 of 116
Figueras-Felip *et al.*[32]	1984	Gentamicin + metronidazole(3) *versus* neomycin + erythromycin(3)	7 of 48 *versus* 2 of 45
Lau *et al.*[33]	1988	Gentamicin + metronidazole(1) *versus* neomycin + erythromycin(3)	5 of 67 *versus* 14 of 62
McArdle *et al.*[34]	1995	Gentamicin + metronidazole(3) *versus* ciprofloxacin(1) + metronidazole(3)	13 of 45 *versus* 4 of 40
McArdle *et al.*[34]	1995	Gentamicin + metronidazole(10) *versus* ciprofloxacin(1) + metronidazole(10)	7 of 42 *versus* 4 of 42
McCulloch *et al.*[35]	1986	Gentamicin + metronidazole(3) *versus* latamoxef(3)	6 of 45 *versus* 5 of 41
Burdon and Keighley[36]	1987	Gentamicin + metronidazole(1) *versus* ceftriaxone(1)	14 of 61 *versus* 5 of 59
Tudor *et al.*[37]	1988	Gentamicin + metronidazole(15) *versus* cefotetan(2)	17 of 75 *versus* 10 of 75
Weidema *et al.*[38]	1985	Gentamicin + metronidazole(4) *versus* metronidazole(4)	4 of 21 *versus* 5 of 20
Greig *et al.*[39]	1987	Gentamicin + metronidazole(1) *versus* gentamicin + metronidazole + cefotetan	18 of 65 *versus* 15 of 64
Lozano *et al.*[40]	1985	Gentamicin + metronidazole(10) *versus* gentamicin + lincomycin(10)	1 of 30 *versus* 3 of 30
Lozano *et al.*[40]	1985	Gentamicin + metronidazole(10) *versus* gentamicin + clindamycin(10)	1 of 30 *versus* 4 of 30
Moesgaard and Nielsen[41]	1988	Gentamicin + metronidazole(2) *versus* gentamicin + metronidazole(7)	22 of 209 *versus* 23 of 219

Fig. 2 Gentamicin plus metronidazole *versus* other antibiotics in preventing surgical wound infection in colorectal surgery. Values in parentheses are number of doses. c.i., Confidence interval



Reference	Year	Antibiotic	Proportion with surgical wound infection
Antonelli *et al.*[42]	1985	Cephalothin(18) *versus* cefoxitin(11)	3 of 30 *versus* 0 of 30
Jones *et al.*[43]	1987	Cephazolin(4) *versus* cefoxitin(5)	1 of 35 *versus* 1 of 36
Jones *et al.*[43]	1987	Cephazolin(4) *versus* cefotaxime(1)	1 of 35 *versus* 4 of 29
Plouffe *et al.*[44]	1985	Cephazolin(3) *versus* latamoxef(3)	1 of 24 *versus* 1 of 26
Thomas *et al.*[45]	1985	Cephazolin + metronidazole(3) *versus* latamoxef(3)	5 of 60 *versus* 3 of 60
Lumley *et al.*[46]	1992	Cephazolin(1) *versus* ceftriaxone(1)	7 of 96 *versus* 7 of 90

Fig. 3 Effect of first-generation *versus* second- or third-generation cephalosporins in preventing surgical wound infection in colorectal surgery. Values in parentheses are number of doses. c.i., Confidence interval

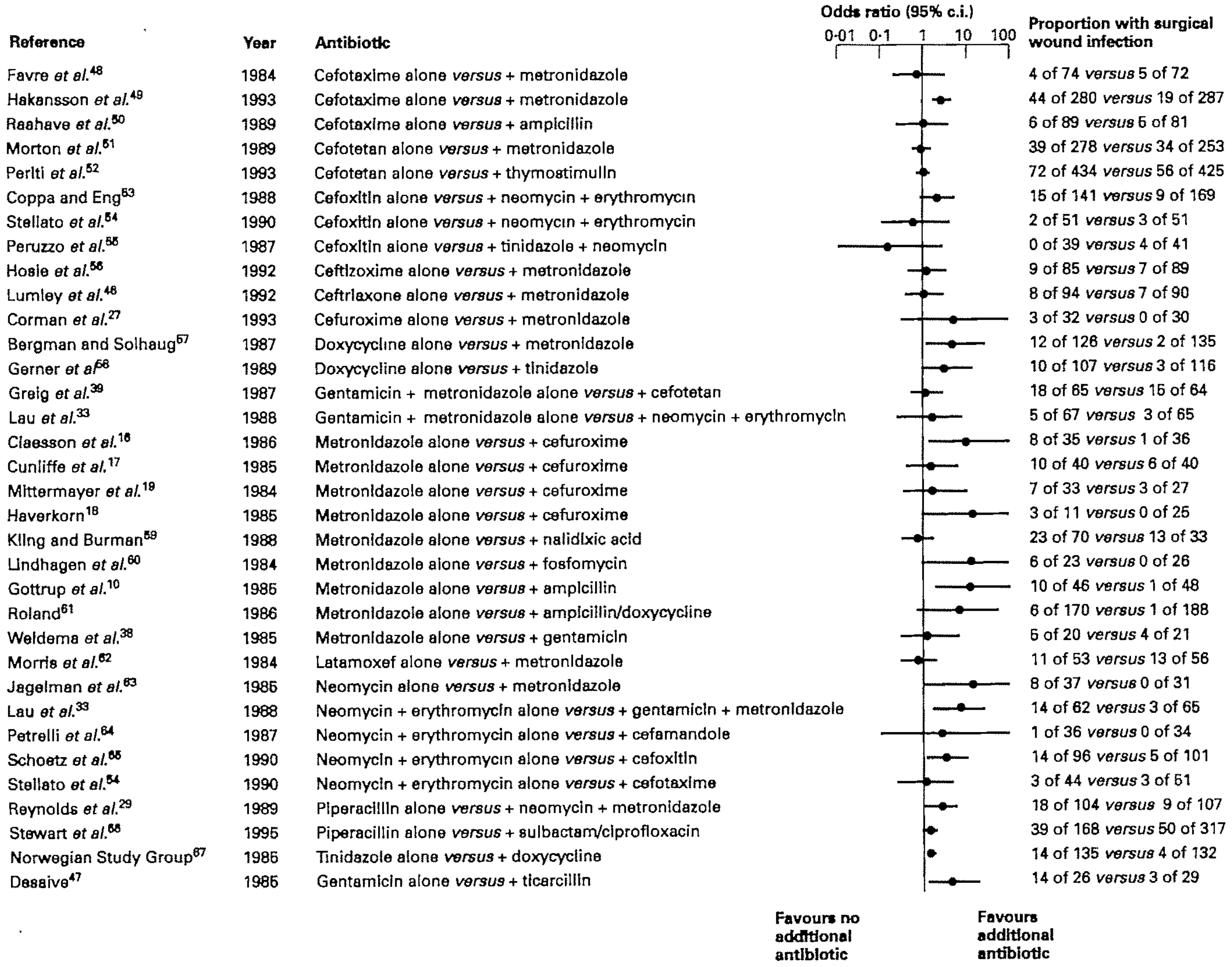
per cent c.i. 1·41–7·23); heterogeneity test, $P = 0·03$)[10,16–19,38,59–61]. The overall rate of surgical wound infection was significantly higher in the oral neomycin plus erythromycin group than in the group treated with neomycin plus erythromycin with additional antibiotics (overall OR 3·34 (95 per cent c.i. 1·66–6·72); heterogeneity test, $P = 0·50$)[33,54,64,65]. It also appeared that the rate of surgical wound infection was significantly reduced when other antibiotics were added to piperacillin (OR 0·57 (95 per cent c.i. 0·38–0·85))[29,66], doxycycline (OR 0·19 (95 per cent c.i. 0·07–0·52))[57,58], cefotaxime (OR 0·50 (95 per cent c.i. 0·31–0·81))[48–50], tinidazole (OR 0·27 (95 per cent c.i. 0·09–0·84))[67] and gentamicin (OR 0·10 (95 per cent c.i. 0·02–0·41))[47]. Conversely, the outcome was not significantly improved when antibiotics were added to gentamicin plus metronidazole[33,39], ceftriaxone[46], cefotetan[51,52], cefoxitin[53–55], ceftizoxime[56] and latamoxef[62].

Single dose versus *multiple doses*

Seventeen trials compared a single-dose regimen with a multiple-dose (two or more doses) regimen using the same antibiotic or combinations of antibiotics (*Fig.* 5)[25,27,31,68–80]. None of these trials found a significant difference in postoperative surgical wound infection between a single- and multiple-dose regimen. When the results from these 17 trials were pooled, there was no statistically significant difference between the single-dose and the multiple-dose group (overall OR 1·17 (95 per cent c.i. 0·90–1·53); heterogeneity test, $P = 0·92$).

Route of administration

Evaluating the relative efficacy of different routes is complicated by the fact that different antibiotics are involved in many trials[29,33,34,39,41,50,53–55,81–89]. Because different antibiotics were used, the importance of the route of administration was not clear when a significant difference between the groups was observed. One trial indicated that oral ciprofloxacin in addition to piperacillin was more effective than piperacillin alone[81]. In another trial, oral ciprofloxacin plus intravenous metronidazole was more effective than intravenous gentamicin plus metronidazole[34]. Greig *et al.*[39] found that cefotetan lavage was no better than saline lavage at the end of the procedure when all patients received preoperative gentamicin plus



Reference	Year	Antibiotic	Proportion with surgical wound infection
Favre *et al.*[48]	1984	Cefotaxime alone *versus* + metronidazole	4 of 74 *versus* 5 of 72
Hakansson *et al.*[49]	1993	Cefotaxime alone *versus* + metronidazole	44 of 280 *versus* 19 of 287
Raahave *et al.*[50]	1989	Cefotaxime alone *versus* + ampicillin	6 of 89 *versus* 5 of 81
Morton *et al.*[51]	1989	Cefotetan alone *versus* + metronidazole	39 of 278 *versus* 34 of 253
Periti *et al.*[52]	1993	Cefotetan alone *versus* + thymostimulin	72 of 434 *versus* 56 of 425
Coppa and Eng[53]	1988	Cefoxitin alone *versus* + neomycin + erythromycin	15 of 141 *versus* 9 of 169
Stellato *et al.*[54]	1990	Cefoxitin alone *versus* + neomycin + erythromycin	2 of 51 *versus* 3 of 51
Peruzzo *et al.*[55]	1987	Cefoxitin alone *versus* + tinidazole + neomycin	0 of 39 *versus* 4 of 41
Hosie *et al.*[56]	1992	Ceftizoxime alone *versus* + metronidazole	9 of 85 *versus* 7 of 89
Lumley *et al.*[46]	1992	Ceftriaxone alone *versus* + metronidazole	8 of 94 *versus* 7 of 90
Corman *et al.*[27]	1993	Cefuroxime alone *versus* + metronidazole	3 of 32 *versus* 0 of 30
Bergman and Solhaug[57]	1987	Doxycycline alone *versus* + metronidazole	12 of 126 *versus* 2 of 135
Gerner *et al*[58]	1989	Doxycycline alone *versus* + tinidazole	10 of 107 *versus* 3 of 116
Greig *et al.*[39]	1987	Gentamicin + metronidazole alone *versus* + cefotetan	18 of 65 *versus* 15 of 64
Lau *et al.*[33]	1988	Gentamicin + metronidazole alone *versus* + neomycin + erythromycin	5 of 67 *versus* 3 of 65
Claesson *et al.*[16]	1986	Metronidazole alone *versus* + cefuroxime	8 of 35 *versus* 1 of 36
Cunliffe *et al.*[17]	1985	Metronidazole alone *versus* + cefuroxime	10 of 40 *versus* 6 of 40
Mittermayer *et al.*[19]	1984	Metronidazole alone *versus* + cefuroxime	7 of 33 *versus* 3 of 27
Haverkorn[18]	1985	Metronidazole alone *versus* + cefuroxime	3 of 11 *versus* 0 of 25
Kling and Burman[59]	1988	Metronidazole alone *versus* + nalidixic acid	23 of 70 *versus* 13 of 33
Lindhagen *et al.*[60]	1984	Metronidazole alone *versus* + fosfomycin	6 of 23 *versus* 0 of 26
Gottrup *et al.*[10]	1985	Metronidazole alone *versus* + ampicillin	10 of 46 *versus* 1 of 48
Roland[61]	1986	Metronidazole alone *versus* + ampicillin/doxycycline	6 of 170 *versus* 1 of 188
Weldema *et al.*[38]	1985	Metronidazole alone *versus* + gentamicin	5 of 20 *versus* 4 of 21
Morris *et al.*[62]	1984	Latamoxef alone *versus* + metronidazole	11 of 53 *versus* 13 of 56
Jagelman *et al.*[63]	1985	Neomycin alone *versus* + metronidazole	8 of 37 *versus* 0 of 31
Lau *et al.*[33]	1988	Neomycin + erythromycin alone *versus* + gentamicin + metronidazole	14 of 62 *versus* 3 of 65
Petrelli *et al.*[64]	1987	Neomycin + erythromycin alone *versus* + cefamandole	1 of 36 *versus* 0 of 34
Schoetz *et al.*[65]	1990	Neomycin + erythromycin alone *versus* + cefoxitin	14 of 96 *versus* 5 of 101
Stellato *et al.*[54]	1990	Neomycin + erythromycin alone *versus* + cefotaxime	3 of 44 *versus* 3 of 51
Reynolds *et al.*[29]	1989	Piperacillin alone *versus* + neomycin + metronidazole	18 of 104 *versus* 9 of 107
Stewart *et al.*[66]	1995	Piperacillin alone *versus* + sulbactam/ciprofloxacin	39 of 168 *versus* 50 of 317
Norwegian Study Group[67]	1985	Tinidazole alone *versus* + doxycycline	14 of 135 *versus* 4 of 132
Dessaive[47]	1985	Gentamicin alone *versus* + ticarcillin	14 of 26 *versus* 3 of 29

Fig. 4 Effect of combinations of antibiotics in preventing surgical wound infection in colorectal surgery. c.i., Confidence interval

Reference	Year	Antibiotic	Proportion with surgical wound infection
Carr *et al.*[68]	1984	Metronidazole(1) *versus* (2-4)	7 of 22 *versus* 11 of 68
Aberg and Thore[69]	1991	Cefuroxime + metronidazole(1) *versus* (3)	2 of 19 *versus* 1 of 29
Corman *et al.*[27]	1993	Cefoxitin(1) *versus* (4)	2 of 31 *versus* 0 of 27
Kow *et al.*[70]	1995	Cefoxitin(1) *versus* (3)	10 of 73 *versus* 8 of 81
Jensen *et al.*[25]	1990	Ampicillin + metronidazole(1) *versus* (3)	14 of 100 *versus* 12 of 104
Juul *et al.*[71]	1987	Ampicillin + metronidazole(1) *versus* (4)	9 of 149 *versus* 8 of 145
Hall *et al.*[31]	1989	Latamoxef(1) *versus* (8)	12 of 119 *versus* 10 of 126
Bates *et al.*[72]	1992	Co-amoxiclav(1) *versus* (3)	23 of 113 *versus* 17 of 111
Grundmann *et al.*[73]	1987	Mezlocillin + metronidazole(1) *versus* (3)	4 of 77 *versus* 4 of 77
Mendel *et al.*[74]	1987	Mezlocillin + metronidazole(1) *versus* (9)	2 of 54 *versus* 1 of 46
Bittner *et al.*[75]	1989	Mezlocillin + metronidazole(1) *versus* (7)	6 of 46 *versus* 3 of 44
Cuthbertson *et al.*[76]	1991	Ticarcillin/clavulanic acid(1) *versus* (2)	16 of 146 *versus* 17 of 132
Kow *et al.*[70]	1995	Cefotaxime + metronidazole(1) *versus* (3)	7 of 84 *versus* 9 of 81
Goransson *et al.*[77]	1984	Doxycycline(1)*versus* (4)	1 of 53 *versus* 2 of 49
Wenzel *et al.*[78]	1985	Gentamicin + metronidazole(1) *versus* (3)	6 of 30 *versus* 10 of 30
Lohr *et al.*[79]	1984	Cefotaxime(1) *versus* (3)	4 of 30 *versus* 3 of 30
Tuchmann *et al.*[80]	1988	Piperacillin + metronidazole(1) *versus* (3)	4 of 61 *versus* 5 of 63

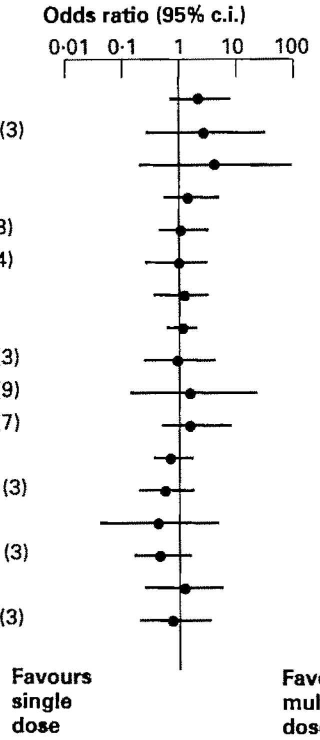


Fig. 5 Effect of single *versus* multiple doses of antibiotic in preventing surgical wound infection in colorectal surgery. Values in parentheses are number of doses. c.i., Confidence interval

metronidazole intravenously. No extra benefit was observed in four trials that compared parenteral alone with parenteral plus topical use of the same antibiotics (12 *versus* 10 per cent; OR 1·13 (95 per cent c.i. 0·60–2·14))[41,87–89]. It seems that oral or topical application of antibiotics is of no added value when appropriate parenteral antibiotics are administered.

Adverse effects

Among the 134 trials that were published in English, 74 (55 per cent) measured and reported results of adverse effects after antibiotic prophylaxis in colorectal surgery. Skin rash, diarrhoea and nausea were commonly mentioned adverse effects that may be attributable to the use of some antibiotic prophylaxis. Patients with a history of allergy to drugs were not included in the trials.

Deaths

In the 42 trials that reported deaths, the total mortality rate ranged from 0 to 16 per cent and was a mean of 4 per cent, similar to the 4·5 per cent reported by Baum *et al.*[90] in 1981. The average death rate in patients undergoing colorectal surgery may have been overestimated by the results from these 42 trials because of potential reporting bias. For example, there might not be any deaths in many of the trials that did not report the mortality results.

Discussion

In this review, the overall rate of surgical wound infection was 11 per cent in patients undergoing colorectal surgery with antibiotic prophylaxis. Baum *et al.*[90] reported that the surgical wound infection rate after colorectal surgery in patients who received antibiotic prophylaxis was a mean of 22 per cent in 26 trials published from 1965 to 1980. In another review by Bartlett and Burton[7], the overall rate was 18 per cent according to 23 trials published from 1960 to 1980. The difference in the rate of surgical wound infection reported in this review compared with that in previous reviews may be due to different definitions of surgical wound infection, different methods of bowel preparation in trials, variation in patient selection, different length of follow-up, different intensity of surveillance or different antimicrobial regimens used.

Surgical wound infection was defined in most trials as 'the presence of purulent discharge' in the surgical wound, with or without positive bacteriology. Swelling and reddening at the wound site and temperature above 38°C were also included as criteria for surgical wound infection[27,69]. Where possible, the authors used abdominal wound infection as the principal outcome measure to compare efficacy of antibiotic prophylaxis. However, in some trials it was not clear whether the wound infection included perineal wound infections and deep intra-abdominal infections.

Several factors were commonly identified to be associated with an increased risk of surgical wound infection in colorectal surgery, such as duration of operation, obesity, the presence of drains, left-sided colonic resection, and inflammatory bowel disease. Two trials reported that the surgeon's experience might be a significant predictor of postoperative wound infection[76,91]. Perioperative blood transfusion was also associated with an increased risk of surgical wound infection in two trials[25,66]. However, a reliable analysis of risk factors is impossible because potential risk factors were measured inconsistently and findings might have been reported selectively.

Because a large volume of bacteria flora is contained in the large bowel, mechanical cleansing is often used to reduce the contents of the colon before the operation. Seventy-eight per cent of included trials stated explicitly that preoperative bowel preparation was carried out. Mechanical cleansing may have been used but was not explicitly stated in the remaining trials.

The majority of included trials compared different regimens of antibiotic prophylaxis. The findings in many trials may not have been statistically significant because the regimens being compared were similarly effective or because the small trials had insufficient power to detect moderate differences. Suppose the rate of surgical wound infection could be lowered by a regimen of antibiotic prophylaxis from 10 to 5 per cent; to detect such a difference at the 5 per cent significance level and 80 per cent power, more than 400 patients would be required in each group[92], a size rarely achieved in the trials considered.

Because the micro-organisms that are potentially responsible for postoperative wound infection after colorectal surgery are diverse, the antibiotics used should be broad spectrum and active against both aerobic and anaerobic bacteria. Additional antibiotics were beneficial when they were added to some regimens such as piperacillin alone, doxycycline alone, tinidazole alone, metronidazole alone and oral neomycin plus erythromycin (*Fig. 4*). However, increased effectiveness was not observed when antibiotics were added to other regimens such as cefoxitin, cefotetan, ceftriaxone, ceftizoxime, latamoxef and gentamicin plus metronidazole. Frequently used antibiotics (such as cefuroxime plus metronidazole and gentamicin plus metronidazole) were adequate compared with other agents (*Figs 1* and *2*).

To be effective against postoperative wound infection, the level of antibiotics in the tissue around the surgical wound should be sufficient at the time of bacterial contamination[93]. Because a single dose of antibiotic appeared to be as effective as multiple doses (*Fig. 5*), it is justified to argue that antibiotic prophylaxis should be used as a single dose or for a short time (e.g. less than 24 h) to reduce the toxicity, cost and the possibility of developing resistant bacteria[94]. The included trials did not provide definitive information about the relation between a single-dose regimen and the duration of operation, although it was often recommended that a second dose is needed if the operation lasts more than 2 h, particularly if the half-life of an antibiotic is short[3,95,96]. In the absence of convincing evidence, clinicians may need to consider other factors, such as perioperative blood loss, to decide whether a second dose of antibiotic is required.

When an antibiotic is administered several hours before the operation, the tissue concentration may not be adequate during operation. For example, oral neomycin plus erythromycin is given from 9 to 20 h before the operation. The main aim is to reduce the risk of bacterial contamination, as a consequence of reducing the bacteria in the large bowel. Some trials showed that oral neomycin and erythromycin on the day before surgery was effective, but further lowering of the rate of surgical wound infection may be achieved by adding parenteral antibiotics just before starting the operation[33,65].

Use of single-dose or short-term antibiotic prophylaxis may reduce selection of antibiotic-resistant bacteria. To be effective, prophylactic antibiotics should be chosen according to the local presence and prevalence of antibiotic-resistant bacteria[97]. For these reasons, it seems right to argue that the search for the ideal prophylactic antibiotic must be a continuous process; universal acceptance and use of a regimen should be avoided[98].

Cost effectiveness

Surgical wound infection is associated with prolonged hospitalization and costly antibiotic treatment. In one study it was observed that superficial surgical wound infection increased the length of stay by a mean of 12·6 days[99]. A study in Scotland found that the median cost to the hospital of a wound infection after colorectal surgery in 1990 was £978 (95 per cent c.i. £484–1521)[100].

The relative cost effectiveness of different regimens needs to be compared to decide which regimen should be selected in the prevention of surgical wound infection in colorectal surgery. Cost-effectiveness ratio is determined by the net cost and the health effect of an intervention[101]. The net cost depends not only on the cost of drugs and their preparation and administration but also on any savings which might be achieved by using antibiotic prophylaxis, such as reduction in hospital stay. When the efficacy and safety of different prophylactic antibiotics is the same, the cost and ease of use become more important[98,102].

Available data indicate that it is possible to reduce the cost of antibiotic prophylaxis without adversely affecting clinical outcome[103–107]. The cost of antibiotic prophylaxis could be reduced, for example, by single-dose or short-term use (less than 24 h after operation) instead of inappropriate long-term use of antibiotics[27,70,108,109]; using more effective and less costly drugs instead of expensive drugs[40,81,110,111]; and using efficacious monotherapy instead of a combination of two or more antibiotics that need to be administered separately[26,30,112].

Antibiotic prophylaxis in surgical practice

Evidence from hospital surveys suggests that inappropriate use of antimicrobial prophylaxis in surgery is common in many countries[113–115]. In an audit of surgical prophylaxis in three hospital trusts in Tayside, Scotland, Davey and colleagues (personal communication; unpublished report by P. Davey, A. Napier, H. Barrie, T. Dodd, J. McMillan, D. Ruta) found that 28 per cent of patients undergoing colorectal surgery received antibiotic prophylaxis for more than 24 h. In a survey of the use of antimicrobial prophylaxis in abdominal and arterial surgery in a district general hospital in England, Dobrzanski *et al.*[105] found that the major problems included no antibiotics at induction (35 per cent), questionable antibiotics at induction (22 per cent), questionable postoperative antibiotics (25 per cent), and unnecessarily long postoperative courses (70 per cent). After introducing guidelines, the use of surgical antibiotic prophylaxis became more appropriate and the cost of antibiotic prophylaxis per surgical patient was reduced from £38·13 to £16·93.

By sending questionnaires to 392 hospitals in the UK, Widdison and colleagues[116] found that formal guidelines were available in 47 per cent of 160 hospitals that responded. Recommended regimens for colorectal surgery included co-amoxiclav (6 per cent), second-generation cephalosporin (2 per cent), metronidazole alone (4 per cent), aminoglycoside plus metronidazole (19 per cent), first-generation cephalosporin plus metronidazole (15 per cent), second-generation cephalosporin plus metronidazole (42 per cent) and other antibiotics (12 per cent). It was claimed that 94 per cent of these regimens included antibiotics with activity against both aerobic and anaerobic bacteria[116].

In a recent survey, Bloxham[117] sent a total of 172 letters to consultant microbiologists in hospitals in the UK. Recommendations on antibiotic prophylaxis in colorectal surgery were available in 49 of 68 antibiotic policies received. Cefuroxime plus metronidazole was the most frequently recommended ($n=28$). Co-amoxiclav was recommended in seven hospital antibiotic policies and gentamicin plus metronidazole in five.

Janknegt *et al.*[118] studied 33 guidelines for antibiotic prophylaxis in surgery used in 89 Dutch hospitals. Compared with guidelines dated before 1991, more after 1991 recommended use of single-dose prophylaxis in colorectal surgery (one of 12 *versus* ten of 20). The antibiotics commonly recommended were active against both anaerobic and aerobic bacteria, including co-amoxiclav, cefuroxime plus metronidazole and gentamicin plus metronidazole.

These surveys of local prescribing guidelines suggest that the use of antimicrobial prophylaxis in colorectal surgery is becoming more appropriate. The majority of antibiotic regimens recommended are active against potential pathogens. An increasing number of guidelines have recommended the use of single-dose prophylaxis. Although efforts are needed to improve and encourage the implemention of existing guidelines, a major concern is that guidelines for antibiotic prophylaxis in colorectal surgery are not available in many hospitals.

Conclusion

The quality of the included trials has improved over the past 12 years, although there were still many methodological problems such as inappropriate patient allocation, lack of blinding during assessment of outcome and insufficient sample sizes.

Antimicrobial prophylaxis is effective in the prevention of surgical wound infection in colorectal surgery. The results suggest that frequently used antibiotics (such as cefuroxime plus metronidazole and gentamicin plus metronidazole) were adequate compared with other agents. Only a limited number of regimens were compared directly and each comparison was evaluated by a limited number of trials. A 'league' table' based on relative efficacy cannot sensibly be constructed. Many different regimens of antimicrobial prophylaxis showed similar efficacy, possibly because of a small difference between regimens and/or a lack of statistical power in trials.

Comparative studies showed that the following regimens are inadequate: metronidazole alone, piperacillin alone, oral neomycin plus erythromycin alone, gentamicin alone, doxycycline alone, cefotaxime alone and tinidazole alone.

The use of a multiple-dose regimen may be unnecessary for the prevention of surgical wound infection; single-dose regimens are as effective and may be associated with less toxicity, fewer adverse effects and less risk of developing bacterial resistance. There is no evidence that new-generation cephalosporins are more effective than first-generation cephalosporins.

Two principles are important to follow when selecting antimicrobial prophylaxis in colorectal surgery: (1) antibiotics or antibiotic combinations should be active against both aerobic and anaerobic bacteria; and (2) the administration of antibiotics should be timed to make sure that the tissue concentration of antibiotic around the wound area is sufficiently high when bacterial contamination occurs.

Further studies of efficacy may be of little value and would require large numbers of patients to demonstrate a statistically significant difference. Future research should focus on understanding the practical use of antimicrobial prophylaxis in colorectal surgery and the cost effectiveness of different regimens. Guidelines should be developed locally in order to achieve a more cost effective use of antimicrobial prophylaxis in colorectal surgery.

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Small bowel obstruction after total or subtotal colectomy: a 10-year retrospective review

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Background The aim of this retrospective study was to determine the cumulative incidence of adhesive small bowel obstruction (SBO) after total or subtotal colectomy and to investigate the site of the obstructive adhesions in the abdominal cavity.

Methods The records of 234 patients who underwent colectomy from 1985 to 1994 were reviewed for SBO, potential risk factors for SBO, and the site of adhesions causing obstruction. Mean follow-up, which was complete in 215 patients, was 63 months.

Results SBO occurred in 56 patients (24 per cent) of whom 42 (18 per cent) had adhesive obstruction. The risk of SBO due to adhesions within 1 year was 11 per cent, increasing to 30 per cent 10 years after colectomy. With univariate analysis no risk factor for adhesive SBO, including previous laparotomies, septic complications and omental resection, was identified. The most common site of obstructing adhesions was the pelvis (ten of 28 patients).

Conclusion The incidence of SBO after colectomy is high. Colectomy may be a suitable model for studies of adhesion prevention.

Adhesions are the commonest cause of small bowel obstruction (SBO) and secondary female infertility, and may be related to chronic abdominal pain. Adhesive SBO is the reason for 1 per cent of admissions in general surgery[1].

The complication rate associated with surgery for adhesive SBO exceeds 50 per cent and the mortality rate is about 10 per cent[2]. In addition, the economic impact of hospitalization for adhesive SBO is enormous[3].

Although almost 100 per cent of patients who undergo laparotomy will develop intra-abdominal adhesions, only a minority will suffer from SBO during their lifetime[4]. It is virtually impossible to predict which adhesions in what patients will cause SBO. This has hampered the study of methods for preventing postsurgical adhesions.

Patients who undergo total or subtotal colectomy seem to carry a high risk of developing SBO[5,6]. For this reason they form an ideal population in which to study preventive measures and pharmacological agents. Risk estimation of SBO after colectomy and knowledge of the sites of obstructive adhesions are essential to conduct such studies properly.

In the present study the time-related incidence of SBO was studied in a 10-year cohort of patients who underwent total or subtotal colectomy. The sites of obstructive adhesions were also assessed.

Patients and methods

A cohort of patients, aged 15 years and older, who underwent subtotal or total colectomy between January 1985 and December 1994 was identified through the hospital information system database.

The medical record of each patient was reviewed for age, sex, diagnosis, length of hospital stay, previous abdominal operations, length and dose of steroid use, type of incision, type of operative procedure, whether or not the omentum was removed or the pelvic peritoneum sutured, duration of operation, amount of blood loss, duration of nasogastric suction, first sign of bowel activity, first oral intake and postoperative complications including death, intra-abdominal abscess, anastomotic leakage, intra-abdominal bleeding and early SBO.

Follow-up data including readmission for SBO, cause of obstruction, number and type of intercurrent laparotomies and cause of death were obtained from the medical records, a questionnaire and telephone interviews with the patients.

The diagnosis of SBO was made from the combination of history (pain, nausea, vomiting, cessation of stool production), physical examination (abnormal bowel sounds, abdominal distension), and abdominal radiography (dilated loops of small bowel, air–fluid levels) findings. At least two of the three specific signs of SBO (acute constipation, high-pitched bowel sounds, dilated loops of small bowel and air–fluid levels on abdominal radiography) had to be present.

Early and late SBO were distinguished. Early obstruction was defined as an obstruction occurring within 4 weeks, and late obstruction as that occurring more than 4 weeks after colectomy[6].

The treatment of SBO and the findings at laparotomy were noted, including the site of adhesions that caused the obstruction.

Statistical analysis

The Mann–Whitney U test and the χ^2 test were used, as appropriate, to compare factors between the groups of patients with and without adhesive SBO respectively. $P < 0{\cdot}05$ was considered statistically significant; all tests were two-tailed.

The Kaplan–Meier product-limit method was used to calculate the cumulative probability of adhesive obstruction. This method calculates incidence curves over time by using follow-up data from all individuals in the cohort, regardless of duration of follow-up. Endpoints of follow-up were the first admission for adhesive SBO, death, loss to follow-up and end of the observational period.

Results

A total of 234 patients underwent total or subtotal colectomy between 1985 and 1994. Subtotal colectomy, leaving the rectum and in some cases a small part of the sigmoid *in situ*, was performed in 100 patients of whom 45

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had an ileorectal anastomosis. Panproctocolectomy was performed in 134 patients followed by ileal pouch–anal anastomosis in 119. Colectomy was performed in 124 men (53 per cent) and 110 female patients (47 per cent) of mean age 40 (range 15–90) years. Indications were ulcerative colitis (140 patients), familial adenomatous polyposis (37), Crohn's disease (19), slow transit obstipation (11), colonic carcinoma (18) and other (nine). In 200 patients (85 per cent) the omentum was resected.

Follow-up by a questionnaire and telephone interviews was complete in 215 patients (92 per cent). Mean duration of follow-up was 63 (range 0·25–144) months.

Twenty-three patients (10 per cent) died: four (2 per cent) early in the postoperative period, ten (4 per cent) as a result of disseminated colonic carcinoma and six (3 per cent) from cardiovascular disease. Three deaths (1 per cent) were related to SBO.

Seventy patients (30 per cent) had undergone previous abdominal surgery with a mean of 1·8 (range 1–11) operations.

Fifty-six patients (24 per cent) were admitted to the hospital for SBO. Eighteen patients were treated conservatively (32 per cent) and 38 underwent laparotomy (68 per cent). In four of 18 patients treated conservatively adhesions appeared to be due to a cause other than SBO, as confirmed by pouch endoscopy or small-bowel follow-through study. Adhesions were the cause of SBO in 28 of 38 patients who underwent operative treatment (*Table 1*).

Early SBO occurred in 13 (23 per cent) of 56 patients. Seven of the 13 patients had adhesive SBO of whom six needed a laparotomy. Forty-two patients (14 treated conservatively and 28 who underwent operation) had obstruction caused by adhesions (18 per cent). This group of patients was analysed further.

Of this group 25 were male (60 per cent) and 17 were female (40 per cent), with a mean age of 37 (range 17–41) years. Demographic factors did not differ significantly between these 42 and the other patients. In particular there was no difference in frequency of omental resection, use of steroids or indication for colectomy (*Table 2*).

The relative number of previous or intercurrent laparotomies was not significantly higher in patients with adhesive SBO than in those without adhesions, and no specific type of surgery increased the risk of adhesive obstruction. An intra-abdominal abscess, anastomotic leak or intra-abdominal bleeding after colectomy did not increase the risk of SBO.

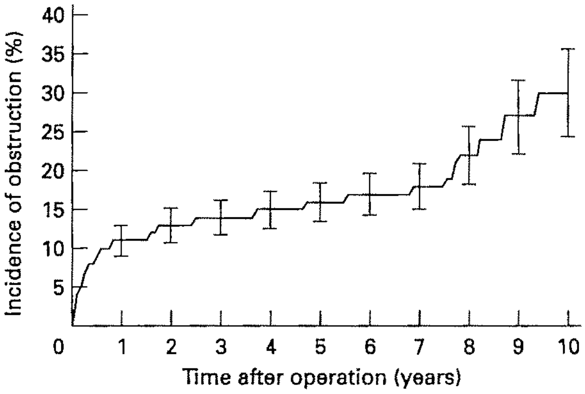
The cumulative incidence of adhesive SBO after (sub)total colectomy is shown in *Fig. 1*. The risk of adhesive SBO within 1 year of colectomy is 11 per cent, increasing to 30 per cent at 10 years.

Table 1 Findings at laparotomy for small bowel obstruction in 38 patients

Finding at laparotomy	No. of patients
Adhesive obstruction	28
Pouch dysfunction	2
Internal herniation	2
Peritonitis carcinomatosa	2
Incarcerated incisional hernia	1
Ileoanal stenosis	1
Unknown	2

Table 2 Incidence of adhesive small bowel obstruction according to indication for colectomy in 234 patients

Indication	*n*	Conservative	Operative	Total
Ulcerative colitis	140	9	18	27
Familial adenomatous polyposis	37	4	4	8
Crohn's disease	19	0	1	1
Slow-transit obstipation	11	0	4	4
Colonic carcinoma	9	0	0	0
Total	234	14	28	42



No. at risk 234 198 185 155 120 90 80 61 43 25 14

Fig. 1 Cumulative incidence of adhesive small bowel obstruction using the Kaplan–Meier method for time-related incidence. This method adjusts the incidence ratio to account for various lengths of follow-up and losses to follow-up. Standard error bars are shown

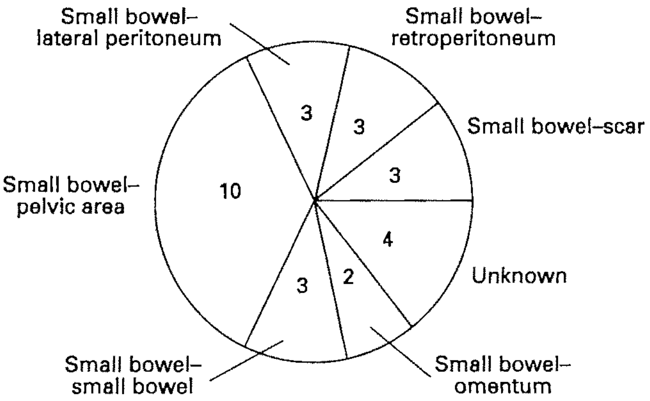


Fig. 2 Distribution of adhesions that caused small bowel obstruction in 28 patients, as identified at laparotomy

The distribution of adhesions found at laparotomy is shown in *Fig. 2*. Obstructive adhesions between small bowel and the lower pelvic area were the most common finding (ten of 28 patients)

Discussion

This is the first study, as far as the authors could determine, in which the occurrence of SBO due to adhesions after subtotal or total colectomy has been analysed in detail and time-related incidence rates of SBO calculated. In previous publications, SBO has been mentioned as a complication after total colectomy, or the incidence of SBO has been assessed in the whole group of abdominal operations below the transverse mesocolon including colectomy, or incidences after right, transverse and left colonic resections have been given separately[5–8]. Fazio and colleagues[6] found SBO in 25·3 per cent and Francois *et al.*[9] in 17 per cent of patients who underwent restorative proctocolectomy and ileal pouch–anal anastomosis with a mean follow-up of 28 months.

In the present series 24 per cent of patients developed SBO, after follow-up much longer than the 2–3-year interval given in the latter reports. This may suggest that SBO is rare more than 2 or 3 years following colectomy; however, approximately 20 per cent of cases of obstruction in the present patients were observed more than 3 years after colectomy. The relatively low incidence of SBO with respect to follow-up may be due to the strict definition of SBO used and the inclusion of patients with malignant disease who have a limited life expectancy and thus a short follow-up period in which to be at risk for developing obstruction.

Kaplan–Meier analysis was first used in a similar retrospective study of the incidence of SBO after cholecystectomy and appendicectomy[10]. In this study 32 per cent of 567 patients were followed, and the observed incidence ratios were much lower than the Kaplan–Meier-adjusted incidences of SBO. In the present study this difference was also present but less pronounced because of the high number of patients with complete follow-up.

Three-quarters of all small bowel obstructions were related to adhesions, both in patients who underwent operation and in those treated conservatively. Obviously, the proportion of SBO caused by adhesions in patients treated conservatively cannot be determined accurately. It is striking that seven of 13 patients had early obstruction due to adhesions, of whom six needed laparotomy. This supports earlier findings that adhesions may pose a serious problem in the early postoperative phase[5].

The omentum may play a protective role by forming 'safe' adhesions to the incisional scar, preventing the more dangerous small bowel adhesions. Omental resection is considered a risk factor for SBO caused by adhesions[11], although this was not evident in the present study or in that of Ambroze *et al.*[12]. Furthermore, prevention of adhesions to the midline incision by a sodium hyaluronate-based bioresorbable membrane (Seprafilm; Genzyme, Cambridge, Massachusetts, USA) did not reduce the incidence of SBO[13]. Whereas it is uncertain whether small bowel adhered to the incision is prone to obstruction, it is accepted that these adhesions increase the risk of iatrogenic small bowel perforations at subsequent laparotomy.

In the analysis, (sub)total colectomy was used as the baseline event for developing SBO, despite the fact that patients had undergone previous laparotomy and/or laparotomy in the follow-up period after colectomy. In comparison with other abdominal operations, surgical damage to the peritoneum is most extensive after colectomy. Conceivably, the fibrinolytic activity of the peritoneum, which is important in reduction of fibrinous adhesions, will be severely diminished after colectomy[14,15]. Although results on fibrinolytic activity in elective abdominal surgery are available, comparison has never been made between surgical procedures with minor and those with major peritoneal damage[16–18].

The pelvis appeared to be the most common site of obstructing adhesions. Herniation and subsequent adherence of small bowel into the narrow pelvis with its bony surroundings might be the mechanism of obstruction. To prevent adherence, several surgical texts advise closure of the parietal peritoneum[19–21]. However, both experimental and clinical studies have shown enhanced adhesion formation and higher incidences of SBO after suturing the pelvic peritoneum[22–24]. The closure of peritoneal defects under tension and the use of reactive suture material in these studies are major points of criticism. Like Irvin and Goligher[25], the present study found no difference in the incidence of SBO due to pelvic adhesions whether the pelvic peritoneum was sutured or left open.

Adhesive intestinal obstruction carries a significant mortality rate[2,26]. As observed by others, elderly patients in particular have a higher mortality rate[7,26]. The relatively young age of patients probably accounts for the lower mortality rate of 7 per cent (three of 42 patients) in the present series, in comparison with that of Jeekel *et al.*[2] (13 per cent) and Treutner and colleagues[26] (15 per cent).

The marked morbidity and mortality rates and the financial costs associated with SBO due to postsurgical adhesions highlight the importance of adhesion prevention[2,3,27]. Recently, new products such as fibrinolytic agents and barrier membranes have been investigated and in part introduced clinically[13,28–31]. From this study it appears that colectomy is a suitable procedure in which to evaluate preventive measures. Prevention should be directed primarily to the areas of dissection, the pelvis in particular.

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Long-term clinical outcome of surgery for solitary rectal ulcer syndrome

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Background When severe symptoms of solitary rectal ulcer syndrome persist despite medical management, surgery may be necessary.

Methods A retrospective review was carried out of 81 patients undergoing surgery for solitary rectal ulcer syndrome in the 10-year period from 1984 to 1993 to determine the long-term outcome at a minimum follow-up of 12 months. Of the 81 patients, 15 were excluded from further analysis (11 were followed up for less than 12 months, two died and two were lost to follow-up). Sixty-six patients were studied (median age 38 (range 15–77) years; 53 female). Of these, 49 underwent rectopexy, nine Delorme's operation, two anterior resection and four creation of a stoma as the initial operation.

Results At a median follow-up of 90 (range 12–177) months, the rectopexy had failed in 22 of 49 patients; 19 of these patients underwent further surgery, including rectal resection with coloanal anastomosis (four with three failures), colostomy (11) and other procedures (four). Ultimately, 14 required a stoma. Constipation was the indication for a stoma in nine of the 11 patients who had colostomy as the first procedure after failure of rectopexy. Nine patients had Delorme's operation as the first procedure. At median follow-up of 38 (range 19–107) months, there were four failures. Two of these ultimately required a stoma. Of the seven patients who underwent anterior resection as the initial or subsequent procedure, a stoma was finally necessary in four. Anterior resection used as a salvage procedure was not successful. The overall stoma rate was 30 per cent (20 patients). Of 11 symptoms assessed before operation only incontinence and incomplete evacuation were related to a poor outcome following surgery.

Conclusion Antiprolapse operations result in a satisfactory long-term outcome in about 55–60 per cent of patients having surgery for solitary rectal ulcer syndrome. Results of anterior resection are disappointing.

Solitary ulcer syndrome is a poorly understood condition. It was recognized in the early nineteenth century[1] and the clinicohistopathological features were described in detail by Madigan and Morson[2]. They demonstrated mucosal thickening with extension of smooth muscle fibres upwards between the crypts. A more recent study of the full-thickness rectal wall has shown architectural abnormalities of the muscularis propria[3]. It is clear that the condition is associated with a disorder of evacuation[4,5], and there is an association with overt rectal prolapse[2,6,7] or internal intussusception[8,9]. The condition is difficult to treat. Medical management consists essentially of measures aimed to facilitate evacuation and prevent straining, but this approach is not always successful, although biofeedback may help in some cases. In a few patients symptoms are so severe that surgery is required. Various operations have been used. They include attempts to deal with prolapse, overt or internal[5,10], excision of the ulcer or defunctioning colostomy. Reports of the outcome of surgery suffer from shortcomings. The condition is rare and numbers of patients are therefore small. Follow-up is usually short. Furthermore, there is little published information on the reoperation rate in patients with solitary ulcer syndrome or the overall failure rate.

In the present study, some of these questions were addressed, with particular reference to the long-term outcome after surgery, the effectiveness of procedures used and the ultimate failure rate judged by stoma formation. This group does not include all patients presenting with solitary ulcer syndrome. Patients treated medically have not been considered and no comment can be made on the effectiveness or otherwise of conservative management.

Patients and methods

The records of patients with a diagnosis of solitary rectal ulcer syndrome operated on between 1984 and 1993 at one hospital were studied. Eighty-one patients who had an operation (excluding surgery for diagnostic purposes only) were identified. Of these, two had died, two were lost to follow-up and in 11, follow-up was less than 12 months. Therefore 15 patients were excluded from further analysis (*Fig. 1*). Many of these had attended the outpatient clinic after operation but the information recorded was not detailed enough to determine the outcome. For six patients there was sufficient information available in the notes; for the remaining 60, details from the notes were supplemented by a telephone interview using a protocol of questions designed to assess the symptomatology before and after surgery. Adequate clinical information was obtained directly in all 66 patients. This included the number of attempts at defaecation per 24 h, the time spent in the toilet during each visit, the fraction of time spent straining while on the toilet, the presence or absence of a persistent desire to defaecate, incontinence, presence of bleeding or mucus, pain and the consistency of stool.

The indication for surgery in every case was severe symptoms not controlled by medical treatment. The choice of procedure depended on the preference of the surgeon but it also changed

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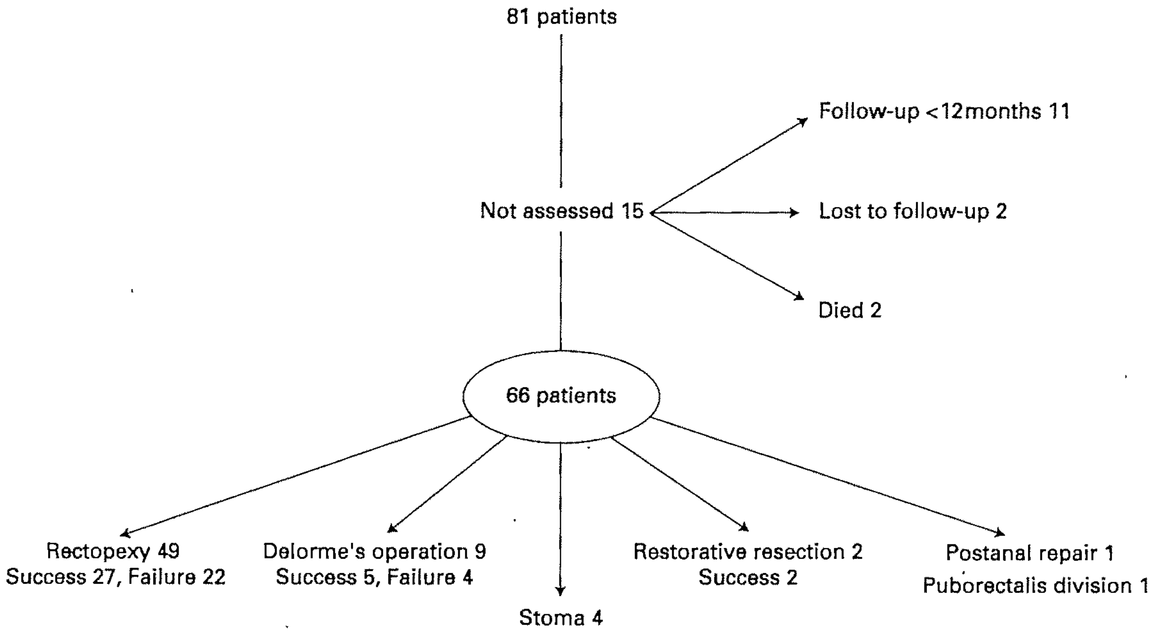

Fig. 1 Outcome of 81 patients having a first operation for solitary rectal ulcer syndrome at St Mark's Hospital from 1984 to 1995

with time. During the early part of the 10-year period, abdominal rectopexy was the commonest procedure but Delorme's operation was being performed increasingly towards the end. The surgical aim was to avoid colostomy as the initial procedure. This was performed rarely as a primary treatment although it was often required following an initial operation for treatment of rectal prolapse.

It is difficult to define precisely the indication for surgery. While there may have been some variation on the part of the surgeon, all patients exhibited failure to respond to medical treatment to the extent that their symptoms were severely restricting their quality of life. Medical treatment was limited to explanation of the need to avoid straining combined with use of suppositories and laxatives to facilitate defaecation. In the last 2 years, biofeedback had been tried. This was available therefore to a small number of patients only.

A successful outcome was defined as the subjective reporting by the patient that the symptoms had completely or substantially resolved following surgery. Failure was defined as the deterioration of symptoms, or no change following the operation. Procedures in patients who had had relief of symptoms for less than 1 year were regarded as failures, as was progression to a further operation for the same condition. The subjective assessment by the patient was correlated with changes in the prevalence of symptoms.

It was not known how many of the 66 patients had undergone preoperative investigations of anorectal physiology and intestinal transit.

Results

The median age of the 66 patients was 38 (range 15–77) years. There were 53 female and 13 male patients. Symptoms had been present before surgery for a mean of 98 (range 5–600) months. A full-thickness rectal prolapse was present at initial presentation in 19 patients. An accurate assessment of morphology could be made from the notes or proctogram report in all patients. Overt ulceration was present in 55 (83 per cent), polypoid change in four (6 per cent) and hyperaemic areas only in seven (11 per cent). A preoperative defaecating proctogram was performed in 50 of the patients and was abnormal in 42 (84 per cent). The commonest abnormalities included the presence of intra-anal or intrarectal intussusception, which was present in 22 (44 per cent), the presence of prominent rectal folds in 12 (24 per cent), abnormal perineal descent in 14 (28 per cent) and slow or incomplete evacuation in 18 (36 per cent). The relationship between these findings and outcome after treatment has already been reported[11]. The median length of follow-up in the 66 patients was 84 (range 19–224) months.

Surgery

The initial operation performed in the 66 patients is shown in *Fig. 1*. The majority had a rectopexy. Four patients had a stoma as the first operation and two a restorative procedure which was successful in both cases. In the earlier years abdominal rectopexy predominated as the antiprolapse procedure of choice. More recently Delorme's operation was used owing to its less invasive nature and in particular the incidence of constipation following rectopexy (see below). The overall success rates for rectopexy and Delorme's operation were similar. No patient in whom the first procedure was successful required further surgery although dilatation of a rectal stricture was necessary in one patient after Delorme's operation. There were no operative deaths.

Rectopexy

Of the 49 patients who had rectopexy, 29 had an anteroposterior fixation, 17 a posterior fixation with insertion of polyvinyl alcohol, one a resection rectopexy and one an anterior rectopexy only; the operative details of one patient could not be found. One patient developed a pulmonary embolus.

The outcome after rectopexy is shown in *Fig. 2*. At a median follow-up of 90 (12–177) months, 22 patients experienced failure, of whom 19 had further surgery. In four patients, a rectal resection with coloanal anastomosis

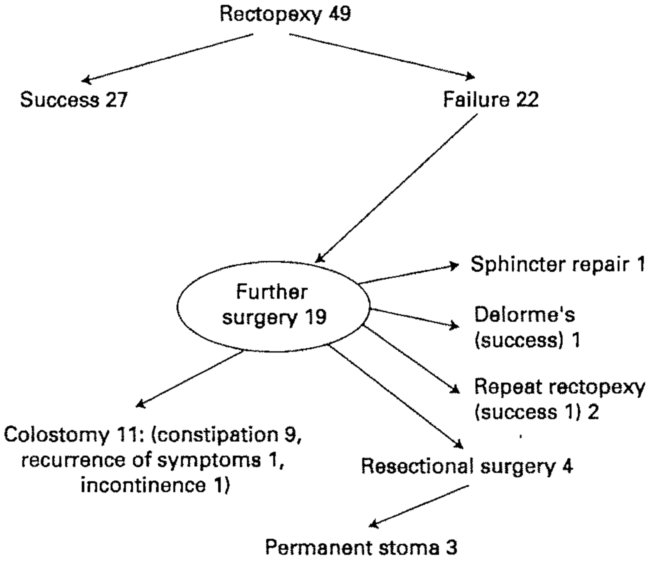

Fig. 2 Outcome of 49 patients having abdominal rectopexy as the initial procedure for solitary rectal ulcer syndrome

was carried out. Three of these failed. In 11 patients, a colostomy was performed. The commonest reason for this was intractable constipation resulting from rectopexy (nine patients). It is noteworthy that Delorme's operation in one patient and and a repeat rectopexy in another were both successful.

The correlation between 'success' and 'failure' judged by the patients' assessment of symptoms before and after surgery from the interview is shown in *Fig. 3*. There was a marked improvement in symptoms when the patient had judged the procedure to be a success. This was less evident when the patient considered the procedure to have failed. Of the 49 rectopexies, 29 resulted in relief or a substantial improvement in symptoms and 20 failed. Ultimately 14 patients required a stoma.

Delorme's operation

Of the nine patients who had this procedure, followed for a median of 38 (19–107) months, four experienced failure (*Fig. 4*). Three of these underwent further surgery. In one patient a rectopexy was performed, which failed. A rectal excision with coloanal anastomosis failed in the second patient and the third received an ileostomy. Of the nine patients, two therefore ultimately required a stoma and five had a satisfactory outcome.

Anterior resection

Anterior resection carried out as the primary procedure in two patients appeared to be successful. It was also used after rectopexy (four patients) and Delorme's operation (one). Four of these patients ultimately required a stoma. In no case was a colonic reservoir added to the reconstruction.

Stoma

A stoma was carried out as the primary procedure in four patients and was subsequently required in 16, 14 after rectopexy and two after Delorme's operation, giving an overall stoma rate of 30 per cent.

Preoperative indicators of outcome

Accurate information on preoperative symptoms was available in 60 of the 66 patients from the hospital notes and interviews by telephone. This was compared with the patients' opinion of whether the operation had been a 'success' or a 'failure'. In this analysis, the four patients treated initially by a stoma were excluded. Data for the remaining 56 patients are shown in *Table 1*. The presence of incontinence and the inability to complete defaecation, determined by the need to revisit the toilet within 15 min

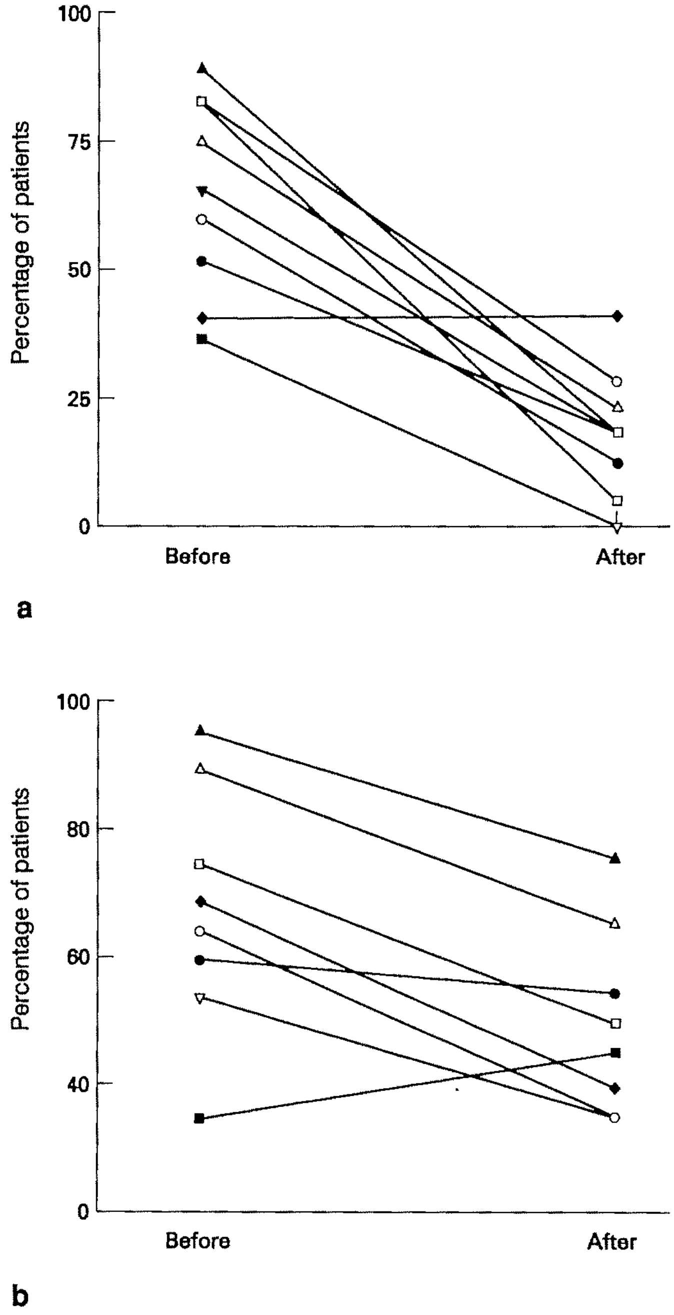

Fig. 3 Change in the percentage of patients having various symptoms before and after rectopexy compared with patients' assessment of success ($n = 27$) (a) or failure ($n = 22$) (b). □, Bleeding; ▲, mucus; ○, pain; △, incomplete evacuation; ◆, straining; ▼, urgency; ●, >15 min in toilet per 24 h; ▽, incontinence; ■, digitation

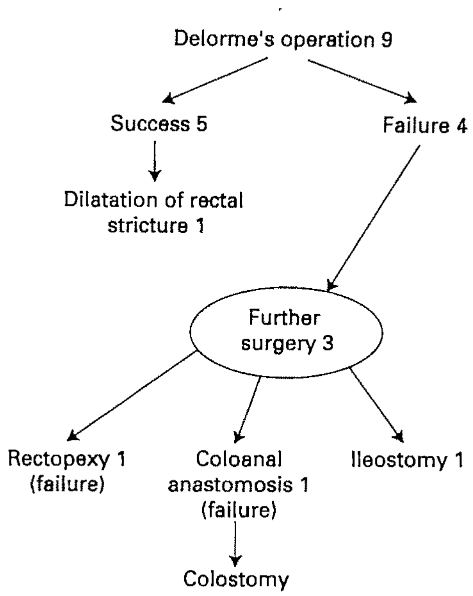

Fig. 4 Outcome of nine patients having Delorme's operation as the initial procedure for solitary rectal ulcer syndrome

Table 1 Relationship between preoperative symptoms and surgical outcome in 56 patients having a stoma-avoiding procedure as the first operation

Preoperative symptom	Success ($n = 33$)	Failure ($n = 23$)
Daily attempts at defaecation (mean)	10·0 (7·3–12·7)	10·7 (7·7–13·8)
Toilet visits lasting more than 15 min	16	14
Straining more than 25 per cent of time in toilet	25	17
Digitation	11	9
Incontinence	10	14*
Inability to complete defaecation	15	17†
Feeling of incomplete defaecation	26	20
Frequent urge to defaecate	25	17
Pain	26	16
Bleeding	30	19
Mucus	30	19

Values in parentheses are 95 per cent confidence intervals. All symptoms were determined at patient interview. Inability to complete defaecation was determined by necessity to revisit the toilet soon after the initial attempt, or by unsuccessful visits. *$P = 0{\cdot}03$, †$P = 0{\cdot}05$ (Fisher's exact test)

of an initial defaecatory attempt, were the only two preoperative factors that could be related to the success or failure of surgery.

Discussion

The patients reported in this study had all received medical treatment. This had failed to control the symptoms, which had become so severe as to require surgery. The series was therefore selected to include the worst sufferers from the condition. The number of patients with solitary ulcer syndrome who did not undergo surgery was unknown, since the hospital documentation system did not record all patients with the condition, whereas every patient who had an operation was identified. Johannsen *et al.*[12] reported that about 15 per cent of patients with rectal intussusception were symptomatically improved by medical treatment and that not all of those in whom therapy failed underwent surgery. It is likely, however, that patients with severe symptoms will require surgery and it is not yet known whether biofeedback will lead to useful relief of symptoms in the long term.

Reports of results of surgery for solitary rectal ulcer syndrome usually deal with small series of patients (*Table 2*) and so the effectiveness of procedures used is difficult to judge. The duration of follow-up is another factor that has not been fully considered when reporting results. In previous publications this is either unstated or short (*Table 2*). It is well known that patients who have surgery for the condition often require subsequent procedures. The present series offers information on the results of surgery, with a reasonably long median duration of follow-up of over 7 years, and reasonable numbers of patients treated, particularly by rectopexy. It has also been possible to quantify the reoperation rate and ultimate stoma rate. These data will be useful when discussing surgery with the patient.

Any retrospective analysis is liable to criticism and there are defects in telephone interviews. A major endpoint of the study is, however, the number and nature of any subsequent procedure, which is a statistic that is completely reliable. The judgement of success or failure of treatment of any functional condition must be made by the patient. It is reassuring that this appears to correlate with the stated improvement in symptoms obtained by interview.

Rectopexy and Delorme's operation are attempts to relieve the symptoms of the condition through treating prolapse. In this, these procedures are reasonably successful. The results of this study show that in the long term about 60 per cent of patients have persisting relief of symptoms following either procedure, with two-thirds of the patients having avoided a stoma. It is not possible from the data available to compare the results of rectopexy and Delorme's operation because numbers of the latter are small and treatment was not randomized. From the available evidence, however, there is no marked difference in outcome between the two procedures. Delorme's operation has the advantage of being less traumatic to the patient. It is, however, not possible to perform in patients in whom the solitary ulcer is associated with a rectal intussusception or where the ulcer itself is surrounded by considerable induration. It may also take several weeks for healing with resolution of pain and discomfort caused by the operation. None of the nine patients developed constipation, however, while this was a severe consequence of nine of the 49 rectopexies.

The failure rate of non-stomal surgery might be reduced by improved case selection. There is evidence from this study that preoperative incontinence or incomplete evacuation are poor prognostic factors. Proctography can contribute to the assessment of prognosis more objectively. Delayed defaecation on proctography or the absence of internal prolapse are both indicators of a poor outcome[12]. That operations directed against prolapse result in relief of symptoms in a high proportion of patients showing evidence of such a defect supports the concept that prolapse is an important factor in the condition. Patients who do not have these features are unlikely to be helped by rectopexy or Delorme's

Table 2 Literature review of surgical series which contain follow-up on ten patients or more

Reference	Year	Operation type	No. of patients	No. of successful procedures	Follow-up (months)
Binnie *et al.*[13]	1992	Transanal excision of ulcer/mucosa	12	(42)	n.a.
		Rectopexy	19	(74)	n.a.
Keighley and Shouler[14]	1984	Rectopexy	14	(50)	12
Nicholls and Simson[10]	1986	Rectopexy	14	(86)	2–48
Schweiger and Alexander-Williams[6]*	1977	Rectopexy	10	(100)	3–13
Stuart[15]	1984	Rectopexy	15	(73)	n.a.
Tjandra *et al.*[16]	1992	Rectopexy	10	(70)	mean 25
		Resection	10	(50)	
Present series	1998	Rectopexy	49	29 (59)	90 (21–177)
		Delorme's	9	5 (55)	38 (19–107)

Values in parentheses are percentages. *All patients had external rectal prolapse. n.a., Data not available

operation and, where surgery is obligatory owing to severity of symptoms, it might be best for the patient to undergo stoma formation as the first operation. This could be reversed later if the patient so wished, although recurrence of symptoms is likely. Patients who complained of inability to complete defaecation before operation also had a high chance of failure after rectopexy and these might also proceed directly to a stoma if all medical attempts have failed.

With only seven patients undergoing anterior resection, it is difficult to draw any firm conclusion about the place of this operation in treatment of solitary rectal ulcer syndrome. However, rectal excision with coloanal anastomosis after a failed rectopexy or Delorme's procedure was unsuccessful in four of five patients. This operation is a major undertaking with a considerable risk of morbidity and it would therefore be reasonable to conclude that patients having a failed rectopexy should be offered a stoma without any subsequent attempt at major restorative resection. In no case was a colonic pouch added to the reconstruction. It is not possible to speculate whether this might have influenced the outcome.

The results of this study will enable the clinician to discuss the likely outcome, enabling the patient to have a useful appreciation of the prospects of success or failure of operations used to treat solitary rectal ulcer.

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Quality of life in patients undergoing treatment for chronic radiation-induced rectal bleeding

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Background Laser and formalin therapy have recently been shown to be safe methods of haemostasis in patients with chronic radiation-induced rectal bleeding (CRRB). The effectiveness of this treatment in terms of improved quality of life remains to be determined. The aim of this study was to develop a questionnaire measure of self-perceived quality of life in patients with CRRB.

Methods A self-completed Rectal Bleeding Quality of Life Scale (RBQOLS) based on the social and emotional problems experienced by patients with CRRB was developed using standard psychometric methods. Before laser and formalin therapy, 34 consecutive patients completed the questionnaire which was repeated 1 month after treatment and again 5 months later. The validity of the scale was assessed in relation to patient response to treatment.

Results The RBQOLS had high reliability (alpha = 0·89) and its concurrent validity was confirmed by a significant association with the pretreatment severity of CRRB assessed endoscopically. The mean RBQOLS score increased from 102 (95 per cent confidence interval 90–114) before treatment to 126 (111–141) after treatment ($t = 3{\cdot}1$, 33 d.f., $P = 0{\cdot}004$) and 136 (122–151) at follow-up attesting to its predictive validity.

Conclusion The RBQOLS is a reliable and valid device for assessing quality of life of patients with this uncommon, previously intractable and potentially life threatening complication of radiotherapy.

Radical external beam radiotherapy is widely used to cure or control various pelvic malignancies, especially of the prostate, cervix or bladder. However chronic radiation-induced rectal bleeding (CRRB) is a complication reported to affect some 5 per cent of radically irradiated patients[1–5]. The incidence of this complication may be increasing with the current trend towards early diagnosis and treatment of prostatic cancer.

Typically the onset of CRRB occurs many months after the completion of radiotherapy and many patients will have had no bleeding during the course of treatment and no identifiable risk factors. For the patient, bleeding is often alarming, usually impossible to anticipate or control, socially inconvenient, physically debilitating and emotionally taxing. It is frequently refractory to treatment using a variety of topical medications and typically runs a protracted course which may lead to transfusion-dependent anaemia. CRRB almost invariably has a marked negative impact on several aspects of the patient's quality of life although an extensive search failed to identify any literature on this subject.

Laser[6–8] and topical formalin[9–11] therapy are safe and effective methods of haemostasis and experience has led to the development of a reliable treatment protocol[12] for patients who have not responded to medical treatment. The aim of this study was to develop a self-completed questionnaire scale for measuring quality of life in patients with CRRB and to assess its validity by applying it to such patients before and after laser and/or topical formalin therapy.

Patients and methods

Patients

This report is based on 34 consecutive patients with CRRB who were treated between October 1994 and April 1996. All had an endoscopic diagnosis of radiation-induced changes, characterized by the presence of multiple telangiectasia confined to the distal 18 cm of the rectum, seen on a background of pale mucosa. All patients presented with intermittent or persistent bleeding of varying severity necessitating iron supplementation or repeated blood transfusion and which had not responded to topical rectal steroids. All were informed of the aims of this study and agreed to participate.

Treatment

Treatment involved either photocoagulation of individual telangiectasias using a class IV neodymium yttrium–aluminium–garnet laser (Laserex SYL5100; Laserex, Adelaide, Australia) or packing the rectum with 4 per cent dilute formalin-soaked ribbon gauze dressings as described previously[12]. Large discrete lesions were destroyed selectively by laser using a low-power setting (20–25 W). Small confluent lesions close to the dentate line in the upper canal were more easily treated with formalin packing administered under a general anaesthetic. The number of treatment sessions varied among patients and therapy was continued until bleeding was controlled, using either or both techniques. Patients were then followed clinically for a minimum of 3 months to ensure that a satisfactory resolution had been attained.

Development of the quality of life scale

Initially the clinical psychologist conducted in-depth interviews with three patients experiencing the typical pattern of symptoms and exemplifying the impact of CRRB on quality of life. The variety and severity of symptoms, the impact of these symptoms on daily life and the emotional response to this condition were

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recorded. From these interviews a number of statements were formulated which appeared to cover the range of symptoms, emotional responses, activity levels and other effects experienced. These statements were then assembled in a self-completed questionnaire in which each statement was accompanied by a line scale with the ends labelled 'constantly' and 'never' and an instruction to patients to mark the line at a point representing the frequency with which they were affected by the symptom or problem as a result of CRRB. Responses were scored from 1 to 10 so that the higher the score the higher the quality of life. The questionnaire was then presented to six typical patients with CRRB in a pretest to eliminate ambiguities and ensure that the format was acceptable and the statements easily understandable. This process resulted in 29 statements which had content validity, which appeared to represent the range of impacts which CRRB has on quality of life, and which could be combined into a summated rating scale[13,14].

Patients completed the quality of life questionnaire immediately before the commencement of laser/formalin therapy, 1 month after completion of treatment and again 5 months later. Patients also completed the Geriatric Depression Scale (GDS)[15] on the same three occasions. This scale is intended as a screening device for depression in elderly subjects and specifically excludes somatic symptoms. On each occasion the questionnaires were administered by the clinical psychologist in the absence of the treating surgeon. The only data missing were a pretreatment haemoglobin level for one patient, post-treatment haemoglobin levels for two patients and a follow-up GDS score for one patient.

Statistical analysis

The significance of the difference between means was assessed by the t test or by the paired t test for correlated observations. The Pearson product-moment coefficient was used to express correlations[16]. The level for statistical significance was 0·05 and confidence intervals are at the 95 per cent level. Factor analysis was by the principal components method with varimax rotation. When used in the development of psychometric scales, factor analysis is a technique for determining whether the individual scale items all belong within the same dimension or realm rather than being distributed among two or more different dimensions[13].

Results

Characteristics of the 34 patients and the prevalence of their symptoms are shown in *Table 1*. *Table 2* describes the nature and extent of radiation-induced changes. Treatment and outcomes are summarized in *Table 3*.

While many of the original 29 quality of life items had a reasonable spread of responses across the range, nine were relatively uncommon (50 per cent or more patients had never or hardly ever experienced them) and these were excluded from further analysis. Factor analysis of the remaining 20 items showed a single predominant factor accounting for 33 per cent of the original total variance. Only three items had low loadings on this factor (understandable in terms of the content of these items) and they were excluded from further analysis. The remaining 17 items all displayed substantial corrected item-total correlations (*Table 4*) and yielded an alpha internal consistency reliability coefficient of 0·89. This set of items is termed the Rectal Bleeding Quality of Life Scale (RBQOLS). The higher the scale score the higher the quality of life. Pretreatment RBQOLS scores ranged from 32 to 163 (mean(s.d.) 102(34)) and were approximately normally distributed (skewness −0·1).

Table 1 Patient characteristics

Sex ratio (M:F)	32:2
Age (years)*	74(5) (62–85)
Reason for radiotherapy	
Carcinoma of the cervix	2
Carcinoma of the bladder	2
Carcinoma of the prostate	30
Onset of bleeding after radiotherapy (weeks)*	43·4(23·3) (8–104)
Bleeding	
Persistent	6
Intermittent	28
Associated symptoms	
Urgency	28
Clustering of defaecation	8
Incontinent to stool	2
Incontinent to mucus	10
Incontinent to flatus	5
Incontinent to blood	19
Passing blood clots	21
Unexpected flooding of blood	11
Pretreatment haemoglobin (g/dl)*	117·5(26·2) (62–162)
Previous medical treatment for bleeding	
Yes	31
No	3
Oral iron	
Yes	7
No	27
Previous transfusion(s)	
Yes	10
No	24
Significant co-morbidity	
Yes	26
No	8

*Values are mean(s.d.) (range). †Not available for one patient

Table 2 Nature and extent of vascular ectasia

Pattern	
Discrete	20
Confluent	8
Mixed	6
Median (range) proximal extent of ectasia from anal verge (cm)	7 (5–25)
Dentate line involved	
Yes	23
No	11
Anal canal involved	
Yes	14
No	20

There was a linear negative correlation between the pretreatment RBQOLS and the GDS ($r=-0{\cdot}59$, 32 d.f., $P=0{\cdot}0002$); the higher the patients' quality of life the less depressed they were. There were statistically significant associations between pretreatment RBQOLS scores and endoscopic findings; a poorer quality of life was reported by patients with a confluent pattern of vascular ectasia compared with those with a discrete or mixed pattern (mean 68 and 112 respectively; 95 per cent confidence interval (c.i.) for difference 21–63) and by those whose changes were circumferential compared with those with predominantly anterior changes (mean 85 and 113 respectively; 95 per cent c.i. for difference 5–51) and these associations were independent of one another. Patients with a confluent pattern of ectasia were also marginally more depressed than those with a discrete or mixed pattern (GDS mean 12·8 *versus* 8·6; 95 per cent c.i. for difference −8·4 to 0·01). There was no association between the RBQOLS and GDS scores and any symptom or other variable in *Table 1*.

Table 3 Laser and/or formalin treatment and outcome

Treatment	
Laser only	3
Formalin only	8
Laser and formalin	23
No. of laser treatments	
1	12
2	12
3	2
No. of formalin treatments	
1	16
2	13
3	2
No. of laser and/or formalin treatments	
1	4
2	12
3	12
4	4
5	2
Duration of treatment (days)*	86 (1–345)
Clinical follow-up after last treatment (months)*	9·1 (3·5–15·9)
Outcome	
Bleeding ceased	28
Occasional minor bleeding continued	6
Post-treatment haemoglobin (g/dl)†‡	123(26) (108–162)
Relapse needing treatment	
Yes	2
No	32

Values are *median (range) or †mean(s.d.) (range). ‡Not available for two patients

Table 4 Items in the radiation-induced bleeding quality of life scale

		Score	Corrected item-total correlation
1	Bleeding/leakage interferes with my daily activities	5·3(2·9)	0·46
2	Because of blood loss I feel short of breath	7·3(3·1)	0·36
3	My bowel problem stops me from doing things I'd like to do	5·3(3·0)	0·35
4	I have to wear a pad for bleeding or leakage	4·9(4·0)	0·38
5	I feel weak and shaky because of blood loss	7·1(3·1)	0·53
6	Bleeding or leakage stops me from going away from my home	7·1(3·2)	0·41
7	I get angry because my bowel problem stops me from doing things I'd like to do	6·7(3·6)	0·72
8	Tiredness because of blood loss stops me from doing things I'd like to do	6·1(3·4)	0·53
9	I have to take special precautions because of the possibility of bleeding or leakage	4·1(3·4)	0·51
10	My bowel problem means that I don't have the energy to do the things I'd like to do	5·6(3·2)	0·71
11	My symptoms (bleeding, tiredness) cause me a lot of inconvenience	4·8(3·0)	0·74
12	I feel useless because my bowel problem stops me from doing the things I want to do	7·4(3·6)	0·72
13	It upsets me to have to take special precautions for bleeding or leakage	5·2(3·8)	0·65
14	Other members of my family are affected by my bowel problem	6·6(3·3)	0·53
15	My bowel problem causes me embarrassment	5·8(3·4)	0·59
16	My bowel problem gets me down	6·4(3·0)	0·43
17	My bowel problem causes me pain or discomfort	6·2(3·4)	0·57

Values are mean(s.d.)

The mean RBQOLS score increased significantly from 102 (95 per cent c.i. 90–114) immediately before treatment to 126 (111–141) at the conclusion of treatment (paired $t = 3{\cdot}1$, 33 d.f., $P = 0{\cdot}004$). There was a further increase to 136 (122–151) at follow-up; however, this was not significantly higher than the post-treatment level (paired $t = 1{\cdot}9$, 33 d.f., $P = 0{\cdot}07$).

The level of depression did not change in response to treatment, the mean GDS score being 9·6 (95 per cent c.i. 7·7–11·4) before treatment, 9·0 (6·7–11·9) after treatment and 9·3 (6·7–11·9) at follow-up. The correlation between RBQOLS and GDS scores increased slightly from $-0{\cdot}59$ (32 d.f., $P = 0{\cdot}0002$) immediately before treatment to $-0{\cdot}75$ (32 d.f., $P < 0{\cdot}0001$) after treatment and $-0{\cdot}67$ (31 d.f., $P < 0{\cdot}0001$) at follow-up.

Discussion

The patient's perspective should be central in monitoring medical care outcomes. As well as providing technically effective treatment a goal of therapy should be to preserve functioning, enhance well-being and ensure a better quality of life. In most circumstances the competent adult patient would be the best judge of whether these latter goals have been achieved, although assessments from the patient's point of view are not made routinely.

The symptoms of CRRB range from inconvenient to devastating and most patients experience a diminution in quality of life. In this study a measure of the quality of life of patients with CRRB was developed, which covered symptoms, practical responses and precautions, impact on activity, family and social life, and emotional and mood reactions such as embarrassment, anger and withdrawal. The authors chose to develop a specific instrument to measure quality of life in these patients rather than use a standard measure because of the peculiar and acute nature of the problems they experience and because a literature search failed to reveal any existing suitable measure. Also patients with CRRB frequently have other physical problems due to advanced age, and it was necessary to design an instrument which would focus on symptoms and problems arising specifically from CRRB rather than from other causes. The resulting set of items appeared to have good content validity and showed excellent scale characteristics including high corrected item-total correlations and a high internal consistency reliability.

A significantly lower pretreatment RBQOLS score was associated with two of the endoscopic observations, namely a confluent pattern of vascular ectasia and a circumferential distribution of lesions. This finding confirms the validity of the RBQOLS as both conditions represent objectively more severe disease, and such patients are more difficult to treat and, in general, experience a poorer quality of life.

The validity of the RBQOLS was further assessed by using it with a group of patients before and after treatment on the hypothesis that the score would increase after completion of treatment. The effectiveness of the treatment protocol in resolving CRRB and eliminating bleeding in a large majority of patients was demonstrated previously[12]. In the present patients therapy continued until effective haemostasis was achieved. There was a significant increase in the RBQOLS score immediately after treatment and a sustained increase 3 months later. This outcome is further evidence for the validity of the RBQOLS.

Depression is the most common psychopathological syndrome affecting the elderly and some somatic symptoms of depression are also characteristic of CRRB, particularly tiredness, lack of energy and social withdrawal. Furthermore CRRB itself is likely to lead to depressed mood and a strong negative correlation was found between quality of life and depression, both before and after treatment. However, treatment produced no change in the level of depression, indicating that quality of life, as measured, was a separate entity from depression, albeit with some overlap between the two.

The RBQOLS is a reliable and valid method for assessing the impact of treatment on quality of life in patients severely incapacitated by CRRB. It has potential for use in randomized controlled trials to evaluate laser and formalin therapy, and other treatment modalities.

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Young age is not a poor prognostic marker in colorectal cancer

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Background There is still considerable controversy and debate regarding the features and prognosis of colorectal cancer in young patients.

Methods One hundred and ten patients (5·1 per cent) under the age of 40 years with colorectal cancer (group Y; male:female ratio 48:62) were compared with 2064 patients with colorectal cancer aged 40 years or more (group O; 917 women, 1147 men). Mode of presentation, stage at diagnosis, tumour characteristics and survival were analysed.

Results Predisposing malignant conditions and family history of colorectal cancer were present in 20·9 per cent of patients in group Y *versus* 2·2 per cent in group O ($P < 0·001$). Common chief complaints included change in bowel habits, bleeding from the rectum and a significantly higher incidence of abdominal pain in group Y. There was no difference in stage at presentation between the two groups (the proportion of Dukes stage A, B, C and 'D' lesions in group Y was 8·2, 24·5, 37·3 and 30·0 per cent respectively *versus* 10·5, 27·9, 33·4 and 28·1 per cent in group O). Tumour site and characteristics were similar in both groups. The incidence of mucinous/signet ring cell and poor grade tumours was 6·9 and 11·8 per cent respectively in group Y and 4·5 and 10·5 per cent in group O. With a mean follow-up of 31·8 months, the overall 5-year survival rate was 54·8 per cent in group Y and 54·1 per cent in group O. Comparing stage for stage, survival was not significantly different in the two groups. However, the adjusted hazard ratios of the age groups Y, M (40–59 years), S (60–79 years), and E (80 years and above) were 1·3, 1 (baseline for calculations), 1·4 and 2·4 respectively, suggesting an adverse outcome for patients in group Y compared with patients aged 40–59 years.

Conclusion This study revealed no difference in tumour characteristics and survival in patients with colorectal cancer aged less than 40 years compared with those aged above 40 years. However, a higher hazard ratio in the youngest group may connote a worse prognosis than that for those aged 40–59 years. A significant family history of colorectal cancer and predisposing conditions in the young warrants aggressive screening, surveillance and treatment of the underlying conditions. The detection of colorectal cancer in young patients should be no different from that in the old but demands a high index of suspicion.

Although cancer of the colon and rectum occurs predominantly in older adults, it does affect young adults with an incidence varying between 1·6 and 23 per cent[1–20]. The behaviour, characteristics and prognosis of colorectal tumours in the young continue to be debated in comparison with those in older patients.

Numerous reports have suggested the unfavourable prognosis of this disease when it occurs in young adults[8,9,11–13,17,18]. This is attributed in most series to the more advanced stage at presentation, postulated to be from delayed diagnosis[10]. Of interest, specific tumour histological features such as the more frequent occurrence of poorly differentiated and mucinous/signet ring cell tumour in the young population may contribute to the poor outcome. However, most studies feature only small numbers of young patients and include no satisfactory comparison group of patients treated during the same period as the young group.

This study was undertaken to determine the incidence of colorectal cancer in young people. The clinical characteristics, frequency of aggressive histological tumour features coupled with stage at presentation and their impact on patient survival were compared with those in older patients.

Patients and methods

The records of 2174 patients who had surgery for primary colorectal cancer in this department over an 8-year period from 1 May 1989 to 30 April 1997 were reviewed from the computer database. The age of 40 years was used to separate the patients into two groups: 'young' (aged under 40 years; group Y) and 'old' (40 years and above; group O). Of these patients, 110 (5·1 per cent) were younger than 40 years. Group O was subdivided into group M (40–50 years), group S (60–79 years) and group E (80 years or more). The diagnosis of colon or rectal cancer was confirmed at operation by the surgeon and by histopathological analysis.

The clinical history recorded for each patient included age at time of operation, sex, predisposing factors (history of familial adenomatous polyposis, hereditary non-polyposis colorectal cancer (HNPCC)[21,22], inflammatory bowel disease, family history of colorectal cancer) and the presenting symptoms.

Staging of disease was according to a modified Dukes classification after operation with review of the pathological specimen and investigations for distant metastases. Histological type was noted in the majority of cases through biopsy or resected specimens. In adenocarcinomas, the tumour histology was subtyped into intestinal, mucinous or signet ring and graded as well

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differentiated, moderate or poor differentiation. The presence or absence of lymphatic, vascular and perineural invasion were also recorded. All histopathological analyses were performed by one gastrointestinal histopathologist.

All patients were followed up 3 monthly for the first year, 6 monthly for the second year and annually thereafter. All surviving patients have had a follow-up period of a minimum of 3 months. Follow-up was available for all but 15 patients.

Two age groups were compared with regard to patients' demographic features, disease stage, tumour characteristics, operation performed and survival. The data of the 110 young patients with colorectal cancer were analysed to determine prognostic factors for survival.

Statistical analysis was done using computer statistical software SPSS version 7·5 (SPSS, Chicago, Illinois, USA). Variables were compared by the χ^2 test. Survival curves were determined by the Kaplan–Meier method and differences in survival were compared by the log rank test. The influence of age on survival was investigated using the Cox proportional hazards regression model, from which estimates of the corresponding hazard ratio and the associated 95 per cent confidence intervals were obtained[23]. The potential influence of the other variables on the relationship with age was investigated by adding these to the Cox model already including age.

Results

Incidence and patients' demography

Patients under the age of 40 years (group Y) with colorectal cancer constituted 5·1 per cent of the 2174 patients operated on for primary colorectal cancer. There were 48 (43·6 per cent) female patients and 62 (56·4 per cent) male patients in group Y. This sex distribution was similar in group O, which had 917 (44·4 per cent) women and 1147 (55·6 per cent) men. The median age of all patients with colorectal cancer was 64 (range 17–100) years. In young patients, the median age was 35 (range 17–39) years.

Obvious predisposing conditions and positive family history of colorectal cancer were found in 23 patients (20·9 per cent) in group Y but only 46 patients (2·2 per cent) in group O ($P < 0{\cdot}001$) (*Table 1*).

The symptoms of the two groups of patients were not significantly different except for abdominal pain which was more prevalent in group Y (*Table 2*).

Tumour characteristics

There was no statistical difference in tumour sites between group Y and group O. The most common sites for cancer occurrence were the rectum and sigmoid colon in both groups of patients. Synchronous cancers were found in 3·6 per cent of patients in group Y and 4·2 per cent of those in group O with an overall synchronous cancer rate of 4·1 per cent.

Tumour type was predominantly adenocarcinoma (88·1 and 94·3 per cent) with more aggressive mucinous and signet ring adenocarcinoma accounting for only 6·9 and 4·5 per cent in groups Y and O respectively. Analysis of tumour differentiation in the two groups did not reveal any significant difference. There was no difference in the stage at presentation between groups Y and O. Other histological variables known to have prognostic influence were found to occur in similar proportions in the two groups (*Table 3*).

Table 1 Predisposing conditions and family history

Family history/ predisposing condition	Group Y ($n = 110$)	Group O ($n = 2064$)
FAP	10 (9·1)	3 (0·1)
HNPCC	9 (8·1)	8 (0·4)
Colorectal cancer	3 (2·7)	35 (1·7)
Ulcerative colitis	1 (0·9)	0 (0)
Total	23 (20·9)	46 (2·2)*

Values in parentheses are percentages. FAP, familial polyposis coli; HNPCC, hereditary non-polyposis colorectal cancer. *$P < 0{\cdot}001$ *versus* group Y (χ^2 test)

Operation performed

Ninety-eight patients (89·1 per cent) in group Y had resection of tumour compared with 1938 (93·9 per cent) in group O. Some 70·0 per cent of the patients in group Y had curative resection compared with 71·0 per cent in group O. A higher proportion of patients in group Y ($n = 11$, 10·0 per cent) underwent restorative proctocolectomy and total colectomy compared with patients in groups O ($n = 32$, 1·6 per cent).

More young patients with colorectal cancer received adjuvant chemotherapy (19·1 *versus* 9·6 per cent in groups Y and O respectively; $P = 0{\cdot}002$) and adjuvant radiotherapy (15·5 *versus* 7·7 per cent; $P = 0{\cdot}007$).

Survival

Univariate analysis in the young patients with colorectal cancer (group Y) revealed significant survival differences for Dukes stage at presentation, tumour differentiation,

Table 2 Presenting symptoms

Symptoms	Group Y ($n = 110$)	Group O ($n = 2064$)	P
Change in bowel habit	75 (68·2)	1423 (68·9)	0·83
Bleeding from the rectum	62 (56·4)	1053 (51·0)	0·28
Weight loss	58 (52·7)	994 (48·2)	0·38
Abdominal pain	49 (44·5)	666 (32·3)	0·01
Mucus from the rectum	18 (16·4)	351 (17·0)	1·00
Abdominal distension	12 (10·9)	280 (13·6)	0·48
Abdominal mass	2 (1·8)	81 (3·9)	0·44

Values in parentheses are percentages.

Table 3 Comparison of Dukes stage at presentation and pathological findings

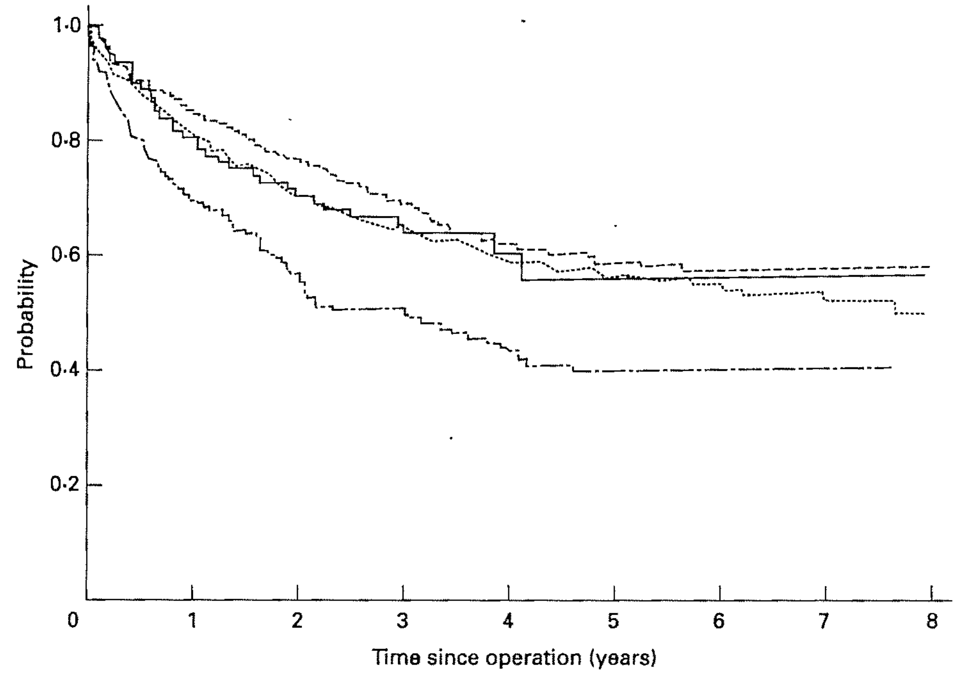
	Group Y ($n = 110$)	Group O ($n = 2064$)	P
Dukes stage			0·67
A	9 (8·2)	217 (10·5)	
B	27 (24·5)	576 (27·9)	
C	41 (37·3)	690 (33·4)	
'D'	33 (30·0)	581 (28·1)	
Tumour differentiation			0·17
Well differentiated	9 (8·8)	97 (4·9)	
Moderate	74 (72·5)	1601 (80·1)	
Poor	12 (11·8)	212 (10·6)	
Mucinous/signet ring	7 (6·9)	90 (4·5)	
Perineural invasion*	19 (18·4)	385 (19·1)	1·00
Lymphatic emboli*	61 (59·2)	1027 (50·8)	0·11
Venous invasion*	6 (5·8)	97 (4·8)	0·63

Values in parentheses are percentages. *Indicates presence of variable in tumour specimen and venous and perineural invasion. Advanced Dukes stage, poor tumour differentiation, and presence of venous and perineural invasion are predictors of poorer survival in young patients with colorectal cancer. Other prognostic variables such as tumour type, site, lymphatic emboli and sex did not have significant impact on survival. There was no death in patients with Dukes A lesions and there were no 5-year survivors among those with Dukes 'D' disease. The 5-year survival rates for patients with Dukes B and C lesions were 85·9 and 65·3 per cent respectively.

Patients in group Y had a 5-year survival rate of 54·8 per cent compared with 54·1 per cent in group O. Stage-for-stage analysis revealed no difference in survival between group Y and group O. Tumour recurrence both locally and distant following curative resection was also compared and there was no significant difference between groups Y and O, for which the 5-year disease-free survival rate was 87·0 and 81·0 per cent respectively.

When stratified by age into groups Y, M, S and E, the survival curves revealed that the elderly (group E) do poorly since the expected years of remaining life are fewer in this group irrespective of disease (*Fig. 1*). Patients in group S had a better prognosis but a poorer outlook than those in the immediately younger group (group M). The survival curve for group Y was closer to that of group S than that of group M (*Fig. 1*).

The hazard ratio for all patients aged less than 80 years is approximately 0·6, suggesting a much lower death rate than that in group E ($\chi^2 = 25\cdot95$, 3 d.f., $P < 0\cdot0001$) (*Table 4*). The hazard ratio for group Y is closer to that of group S than that of the immediately older patients in group M. However, the confidence intervals for the corresponding hazard ratios are overlapping and so a differential



No. at risk (deaths)

Y	110(0)	73(20)	55(9)	42(5)	29(2)	18(2)	9(0)	4(0)	0(0)
M	691(0)	487(99)	365(45)	246(35)	182(23)	105(15)	63(2)	23(0)	1(0)
S	1142(0)	794(211)	585(94)	428(50)	307(32)	202(9)	119(5)	43(4)	1(1)
E	216(0)	127(63)	88(22)	58(9)	37(8)	22(3)	11(0)	4(0)	0(0)

Fig. 1 Survival by age group. ———, Group Y (<40 years); — — —, group M (40–59 years); ...., group S (60–79 years); —·—·—, group E (≥80 years)

Table 4 Hazard ratios by age group calculated using a Cox model

Age (years)	Group	No. of patients	No. of deaths	Regression coefficient	Standard deviation	Hazard ratio
<40	Y	110	38	−0·51	0·19	0·60 (0·41–0·87)
40–59	M	691	213	−0·64	0·12	0·53 (0·42–0·67)
60–79	S	1142	412	−0·48	0·11	0·62 (0·50–0·77)
≥80	E	216	105	0	—	1
Total		2159	768			

Values in parentheses are 95 per cent confidence intervals

Table 5 Adjusted hazard ratios by age group using a Cox model

Age (years)	Age group	No. of patients	No. of deaths	Regression coefficient	Standard deviation	Hazard ratio
< 29	Y	23	9	0·23	0·35	1·26 (0·64–2·48)
30–39	Y	87	29	0·23	0·22	1·26 (0·83–1·93)
40–49	M	244	76	0	0·15	1·00 (0·75–1·34)
50–59	M	447	137	0	—	1 —
60–69	S	629	193	0·10	0·12	1·10 (0·87–1·38)
70–79	S	513	219	0·42	0·11	1·53 (1·23–1·91)
80–89	E	204	99	0·81	0·14	2·25 (1·72–2·94)
≥ 90	E	12	6	1·18	0·46	2·94 (1·20–7·20)
Total		2159	768			

Values in parentheses are 95 per cent confidence intervals

prognosis for the Y, M and S groups cannot be reliably concluded, although the risk of death in all these groups is significantly less than that for group E.

Adjusted analyses, which were undertaken by adding univariate predictors of poor prognosis (Dukes stage at presentation, tumour differentiation and evidence of perineural invasion) sequentially to the Cox model already including age, gave age group hazard ratios of 0·53, 0·42 and 0·56 respectively. There were too few patients in group Y to adjust for the presence of venous involvement. In this analysis, patients in group M had the best prognosis, using these as the baseline for hazard ratio calculations (hazard ratio 1), the corresponding values for groups Y, S and O were 1·3, 1·4 and 2·4 respectively. This suggested lowest risk among patients in group M (aged 40–59 years) was further explored by a Cox model using the stratified decade age groups. The single patient under 20 years of age was combined into the 20s age group. The hazard ratios relative to what appears to be the most favourable prognosis group (patients in their 50s) are shown in *Table 5*. Although this suggests a convex relationship of the risk of death associated with age, with the youngest patients having a somewhat worse prognosis than might be anticipated, their risk is similar to that of the median age group of patients with colorectal cancer, and only patients of 70 years or more have a significantly increased risk of death.

Discussion

Cancer of the colon and rectum is the second most frequent cancer in men and women in Singapore[24]. There is a mean annual increase of 3·84 and 2·73 per cent age-standardized rate of colon and rectum cancer respectively in men and 4·08 and 2·23 per cent respectively in women. Colorectal cancer is projected to overtake lung cancer as Singapore's most common cancer by the turn of the century.

The interpretation of survival data from small series collected over long periods of time is subject to many biases. During a long time period, it is likely that treatment protocols may change and that patients in these series have not all been managed in the same way. Singapore has one of the highest age-adjusted incidence rates for colorectal cancer in the world[25] and thus arguably a 'high-risk' population would be a good place to analyse this controversy.

Inherent to the discussion are the possible explanations for the unfavourable prognosis of the young patients with colorectal cancer. In larger series reviewed, there is a greater proportion of poor prognostic tumour variables, such as mucinous or signet ring cell and poor grade tumours, in the young than in the old. Other histopathological indicators of aggressive tumour biology include infiltrating tumour edge, and venous, perineural and lymphatic invasion[20]. There was no difference in any of these tumour variables between young and old patients in the present series, in contrast to most if not all published results to the authors' knowledge.

Delayed diagnosis, which may explain the higher rate of advanced disease at presentation in the young, has been disputed. Several investigators contend that the late diagnosis, attributed to low vigilance, contributes to this discrepancy in the young[13,26]. However, duration of symptoms may not predict survival from diagnosis[1,20], because of lead time bias of the more aggressive tumour[7,27]. The presenting complaints of colorectal malignancy in the young and old are the same and thus should not detract from making an accurate diagnosis. However, the suspicion of malignancy in the young is low and symptoms such as abdominal pain or change in bowel habit should not be regarded lightly. In this series, abdominal pain occurred in a significantly higher percentage of young than old patients which is consistent with other series[2,13,28]. Granted that this age group has a high proportion of patients with irritable bowel syndrome, which may not require much investigation, a high index of suspicion among this age group cannot be overemphasized to prevent a delayed diagnosis.

Stage is the most common reproducible independent variable affecting prognosis. In most series, be it the result of aggression of the tumour itself or delay in diagnosis, the young seem to have more advanced stage tumour at presentation than the old. However, the distribution of stage at presentation in this series was similar between the two age categories. The reason could be the aggressive screening and surveillance among the young especially if there is a positive family history through the Polyposis Registry[29], thus allowing detection of a higher percentage of tumours at an early stage at presentation.

The short follow-up in the current study required the use of hazard ratios to estimate risk of death. While the youngest patients may have a greater risk of death than expected, the prognosis for patients aged less than 40, 40–59 and 60–79 years was not significantly different. It may become more apparent whether young age is a poor prognostic marker as these patients are followed up for a longer period of time.

The results of this analysis indicate that patients under 40 years of age with colorectal cancer have tumour characteristics and stage at presentation similar to those of older patients. In both overall and stage-for-stage comparison, they have comparable if not better survival outcome. Young age with colorectal cancer is not a poor major prognostic factor and therefore should not be regarded with pessimism. Known predisposing factors such as polyposis coli, HNPCC, ulcerative colitis and also a strong family history of colorectal cancer were a strong feature in young patients. This underlines the importance of family screening, aggressive surveillance and treatment in the young with known predisposing conditions. Coupled with a high index of awareness in these patients with symptoms suggestive of malignancy, surgical treatment should be radical and optimized with adjuvant therapy where possible to achieve the best prognosis.

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Improved outcome after emergency surgery for cancer of the large intestine

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Background Emergency surgery for colorectal cancer has become more aggressive and radical over the past decade. This retrospective review analyses the impact on outcome.

Methods The results of emergency surgery within 24 h of admission were compared between 1982 and 1987 (77 patients) and 1988 and 1993 (75 patients). Patient and tumour characteristics were similar in both groups.

Results Right colonic obstruction or perforation was treated by primary resection and anastomosis in 11 of 12 patients before 1988 and in all 19 patients thereafter. Primary resection was also the treatment of choice for perforated cancer of the left colon and rectum before 18 of 20) and after (20 of 21) 1988. The rate of primary resection for obstructing cancer of the left colon and rectum increased from 17 of 45 to 30 of 35. One-stage resections for obstructing cancer were performed in ten of 45 and 22 of 35 patients before and after 1988 respectively. The overall mortality rate declined from 14 of 77 to three of 75 after 1988 ($P < 0{\cdot}01$). The rate of radical lymphadenectomy rose from six of 46 patients to 42 of 69 after 1988. The 3-year survival rate increased from 50 to 74 per cent ($P < 0{\cdot}05$).

Conclusion The data support further efforts towards improving the immediate and late outcome of emergency surgery in complicated colorectal cancer.

Over 15 per cent of colorectal carcinomas present as acute colonic perforation or obstruction despite cancer-screening programmes and routine endoscopy[1–4]. Surgical emergencies are associated with high morbidity and mortality rates and a low cure rate. Safety considerations have led surgeons to perform mainly minimal procedures consisting of colostomy followed by resection and colostomy closure. This traditional three-stage operation was gradually replaced by a two-stage (Hartmann's) operation or even a single-stage procedure in many centres, although studies failed to demonstrate a survival benefit from primary resection[1,5–7]. Despite strong arguments in favour of primary resection and anastomosis in complicated colon cancer, recent surveys of the literature did not provide clear guidelines based on existing data[3,4,8].

This study analysed emergency surgery within 24 h of admission between 1982 and 1993. During this period, primary resection replaced initial decompression in this unit and radical lymphadenectomy was increasingly performed as part of the emergency procedure. To study the impact of these changes on immediate and late outcome, results of the first 6-year period (1982–1987) were compared with those of the second (1988–1993).

Patients and methods

The clinical data, including the timing of operation, were collected prospectively in the Heidelberg Tumor Registry for 1944 patients with colorectal cancer. Follow-up was carried out according to a standard protocol. Patients were followed up until death or the end of the observation period (December 1996; median 67 months). Twelve patients (1 per cent) could not be followed up and were included in the survival analysis as a censored observation. Emergency surgery within 24 h of admission was confirmed by the patient records, thus excluding all elective or urgent cases. Hospital records provided the following variables: age, sex, tumour stage and location, surgical treatment, postoperative morbidity and mortality rates, and long-term survival.

Between 1982 and 1993, 1944 patients underwent surgical treatment for primary colorectal carcinomas: 920 between 1982 and 1987 and 1024 between 1988 and 1993. Detailed data for 923 patients from the 1982–1987 period have already been published[9]. This slight discrepancy (920 *versus* 923 patients) and subsequent changes in the patient analysis resulted from a different computer registration of patients in December 1981 and 1987. Emergency laparotomy within 24 h of admission was performed for large bowel obstruction or perforation in 152 patients (8 per cent). The other 1792 patients (92 per cent) were considered elective cases in this study.

Tumour staging followed the postoperative histopathological tumour node metastasis (pTNM) classification of the Union Internacional Contra la Cancrum (fourth edition, second revision, 1992) which is fully compatible with the fourth edition of the American Joint Committee on Cancer staging system. The tumour stage was revised and reclassified if necessary.

Two-tailed Fisher's exact test was used for the statistical comparison of patient subgroups. The statistical yield of this study was overall survival from the date of surgery. Cancer-related deaths were the events of interest for survival analysis. All other observed survival times were (right) censored. Overall survival rates were calculated by the Kaplan–Meier method. The log rank test was used to analyse the difference between survival curves. Features independently associated with overall survival were identified in multivariate analysis by proportional risk regression using the software program SAS 6.10 (SAS Institute, Cary, North Carolina, USA). Step-down regression methods were used to set up parsimonious statistical models for relating prognostic factors to the overall survival of patients with complete data[10].

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Results

Patients and tumour characteristics

Of the 152 emergency laparotomies within 24 h of admission, 111 were performed for obstruction and 41 for perforation; there were ten combined procedures. The 7–8 per cent rate of emergency colorectal carcinoma surgery remained fairly constant over time. Age distribution was similar before (median 78 (range 41–97) years) and after (median 76 (range 45–92) years) 1988. There was a shift towards female preponderance in the emergency groups in the last few years from 49 to 65 per cent.

Obstruction and perforation occurred most frequently in cancer of the left colon (*Table 1*). Tumour location did not differ statistically between the two observation periods. The tumour stages showed no significant variation in the obstruction and perforation groups. An increased frequency of higher tumour grades was found in the perforation groups (two of 18 *versus* 12 of 20; $P = 0.036$) but not in the obstruction groups (four of 41 *versus* 13 of 51; $P = 0.060$).

Surgical management

The overall primary resection rate within 24 h of admission increased from 60 per cent (46 of 77) in the 1982–1987 period to 92 per cent (68 of 75) between 1988 and 1993 ($P = 0.007$). Limited segmental resections were the procedure of choice before 1988, being performed in 40 of the 46 patients. Only six underwent primary radical surgery including monoblock lymphadenectomy with central ligation of the main colonic vessels (e.g. inferior mesenteric artery for left-sided cancer, ileocolic and right colic artery for right-sided cancer). After 1988, radical surgery became increasingly accepted as an initial procedure and was performed in 42 (61 per cent) of 69 patients. These included mainly patients without metastasis: 35 of 36 patients with obstructing and seven of 16 with perforating carcinomas. Complete (curative) tumour eradication was achieved in 53 per cent (41 of 77) and 60 per cent (45 of 75). Details of the surgical procedures are presented in *Table 2*.

Primary resection for obstructing cancer was performed in 28 (49 per cent) of 57 patients before and in 49 (91 per cent) of 54 patients after 1988 ($P < 0.001$). For cancer located in the right colon, therapy consisted of primary resection plus anastomosis for both observation periods (11 of 12 *versus* 19 of 19). The operative concept for obstructing cancer of the left colon and rectum changed over time. Emergency resection with and without anastomosis was performed in 17 of 45 patients before 1988 and in 30 of 35 thereafter ($P < 0.001$). Single-stage resections were performed in ten of 17 patients before and 22 of 30 patients after 1988 ($P < 0.34$); a one-stage resection was therefore carried out in ten of 45 and 22 of 35 patients respectively ($P < 0.001$).

In perforating cancer, primary resection, peritoneal lavage and drainage was the treatment of choice in both observation periods irrespective of tumour location. Eighteen of 20 perforating lesions were resected before 1988 and 20 of 21 thereafter. Bowel continuity was restored by primary anastomosis in eight of nine emergency right hemicolectomies before and in all five operations after 1988. All nine perforating tumours of the left colon and rectum from 1982 to 1987 and 13 of 15 such lesions from 1988 to 1993 were managed by Hartmann's operation.

Of the 37 initial decompression procedures within 24 h of admission, only 15 were completed by staged resection. Secondary resection was performed in 13 of 31 patients before and two of six patients after 1988. This failure to complete the planned sequence of operations resulted in a permanent stoma in 15 of 30 survivors.

In the 1982–1988 period, eight of 35 patients with primary resection and anastomosis had a protective enterostomy. However, this concept was abandoned in the late 1980s and was used only twice in 49 patients after 1988. It was replaced by the intraoperative colonic lavage technique with primary anastomosis introduced in the mid-1980s. As a consequence, intraoperative colonic lavage for obstructing left-sided colon and rectal cancer was used in four of 45 patients before 1988 and 25 of 35 after 1988.

Table 1 Tumour characteristics (after resection)

	Obstruction		Perforation	
	1982–1987 ($n = 41$)	1988–1993 ($n = 51$)	1982–1987 ($n = 18$)	1988–1993 ($n = 20$)
Tumour stage (UICC)				
I	2	0	1	0
II	13	19	11	6
III	17	17	2	10
IV	8	15	3	3
Unknown	1	0	1	1
Grade				
I/II	36	38	12	8*
III/IV	4	13	4	12
Unknown	1	0	2	0
Localization				
Right colon	12	19	9	5
Left colon	28	29	8	11
Rectum	1	3	1	4
Unknown	0	0	0	0

UICC, Union Internacional Contra la Cancrum. *$P < 0.05$ *versus* 1982–1987 group (Pearson χ^2 test)

Table 2 Emergency surgery within 24 h after admission and postoperative deaths (in hospital) in relation to tumour location

Emergency situation	Tumour location	Time interval	Primary resection	Primary decompression	
				Staged resection	Diversion only
Obstruction	Right colon	1982–1987	11 (3)	1 (0)	—
		1988–1993	19 (0)	—	—
	Left colon	1982–1987	17 (1)	11 (0)	10 (3)
		1988–1993	27 (1)	2 (0)	1 (1)
	Rectum	1982–1987	—	1 (0)	6 (1)
		1988–1993	3 (0)	—	2 (0)
Perforation	Right colon	1982–1987	9 (2)	—	—
		1988–1993	5 (1)	—	—
	Left colon	1982–1987	8 (2)	—	2 (2)
		1988–1993	11 (0)	—	—
	Rectum	1982–1987	1 (0)	—	—
		1988–1993	4 (0)	—	1 (0)

Values in parentheses are number of deaths

Early outcome

The overall postoperative complication rate following emergency surgery was high throughout the entire observation period. The overall hospital mortality rate dropped from 18 per cent (1982–1987) to 4 per cent (1988–1993) ($P = 0{\cdot}008$). Following primary resection, eight of 46 patients died before 1988 and two of 69 after 1988. After emergency decompression colostomy, six of 31 patients died between 1982 and 1987 compared with one of six patients between 1988 and 1993.

Following malignant obstruction, postoperative peritonitis and cardiac decompensation were the most frequent and fatal complications in both periods. Not only the frequency of these complications but also the mortality rate decreased dramatically over time. Postoperative cardiac failure was usually due to persisting ileus and typically associated with primary decompression procedures. The incidence of fatal cardiac failure declined from five to one after 1988 as the number of decompression procedures decreased from 29 to five. Another serious complication was anastomotic failure. In the 1982–1987 observation period, there were three anastomotic leaks (one ileocolonic and two colocolonic; two fatal) after 21 primary anastomoses and one additional fatal leakage after appendicectomy for insertion of the orthograde irrigation device. In contrast, there were only two non-fatal leaks (both colocolonic) after 41 primary anastomoses between 1988 and 1993.

Morbidity after malignant perforation was high throughout both observation periods. Residual peritonitis and prolonged severe sepsis occurred in four of 20 patients before 1988, all of whom died, and in four of 21 patients between 1988 and 1993 with only one death.

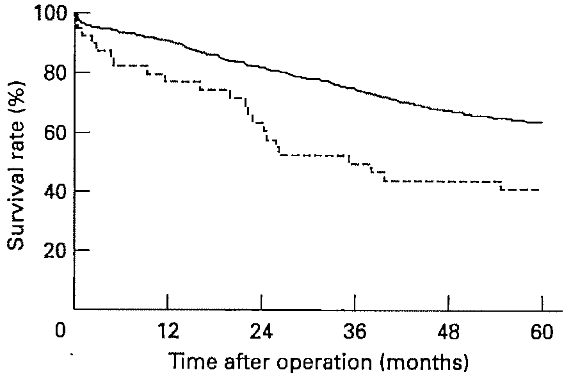
Late outcome

The median observation period was 67 months (1982–1987, 113 months; 1988–1993, 49 months) with a minimum of 36 months. The overall prognosis after emergency surgery was poor. Many patients with advanced cancer died soon after discharge from hospital. This resulted in a low survival rate after 2 months (*Table 3*). Long-term survival after curative resection was significantly worse after emergency than after elective surgery (*Figs 1* and *2*). However, survival rates improved over time. The 3-year survival rate after curative resection significantly increased from 50 per cent before 1988 to 74 per cent after 1988 (*Table 3*). This was mainly due to improved outcome after obstruction (56 *versus* 81 per cent). However, the difference in 5-year survival after

Table 3 Postoperative deaths and long-term survival

	Emergency surgery (total)		Obstruction		Perforation	
	1982–1987 ($n=77$)	1988–1993 ($n=75$)	1982–1987 ($n=57$)	1988–1993 ($n=54$)	1982–1987 ($n=20$)	1988–1993 ($n=21$)
Hospital deaths*	14 (18)	3 (4)	8 (14)	2 (4)	6 (30)	1 (5)‡
Deaths within 2 months*	18 (23)	11 (15)	12 (21)	6 (11)	6 (30)	5 (24)
Overall 3-year survival (%)†	29 (20–38)	45 (35–55)	31 (20–41)	52 (41–64)	25 (9–41)	28 (11–45)
Overall 5-year survival (%)†	23 (15–31)	29 (19–39)	26 (16–37)	29 (18–41)	15 (2–28)	28 (11–45)
3-year survival after curative resection (%)†	50 (37–63)	74 (63–85)	56 (40–68)	81 (70–93)	36 (13–60)	50 (24–76)
5-year survival after curative resection (%)†	41 (28–55)	47 (33–61)	47 (31–63)	41 (30–62)	27 (5–49)	50 (24–76)

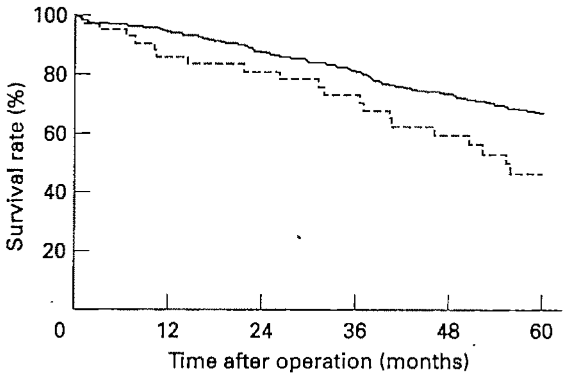
Values in parentheses are *percentages or †95 per cent confidence intervals. ‡$P < 0{\cdot}05$ *versus* 1982–1987 (Pearson χ^2 text)



No. at risk

	0	12	24	36	48	60
Elective	618	562	505	455	404	374
Emergency	41	30	23	18	16	13

Fig. 1 Life-table analysis (Kaplan–Meier estimates) for patients with colorectal cancer resected curatively between 1982 and 1987. ———, Elective surgery; - - - -, emergency surgery (within 24 h after admission). ($t = 16·24$, 1 d.f., $P < 0·001$; log rank test)



No. at risk

	0	12	24	36	48	60
Elective	667	614	544	422	301	199
Emergency	45	38	32	28	20	10

Fig. 2 Life-table analysis (Kaplan–Meier estimates) for patients with colorectal cancer resected curatively between 1988 and 1993. ———, Elective surgery; - - - -, emergency surgery (within 24 h after admission). ($t = 10·11$, 1 d.f., $P = 0·0015$; log rank test)

Table 4 Influence of patient and tumour characteristics on overall survival for colorectal cancer following curative resection

	1982–1987 (*n* = 659)				1988–1993 (*n* = 710)			
	n	No. alive	5-year survival (%)	*P*	*n*	No. alive	5-year survival (%)	*P*
TNM stage (UICC)								
I	208	135	77		197	165	84	
II	216	112	66		250	183	67	
III	207	97	48		236	144	54	
IV	15	2	27	< 0·001	22	6	24	< 0·001
Grade								
I/II	519	294	65		546	405	70	
III/IV	103	43	51	< 0·002	153	88	51	< 0·001
Median age (years)								
≤ 66·2	305	186	70		381	304	71	
> 66·2	354	167	57	< 0·001	329	219	60	< 0·001
Sex								
Male	342	161	56		402	282	67	
Female	317	192	70	< 0·001	308	221	65	0·93
Surgery								
Elective	618	339	64		667	483	68	
Emergency	41	14	41	< 0·001	43	20	47	0·0015
Tumour location								
Colon	381	207	64		380	271	66	
Rectum	278	146	61	0·49	330	232	67	0·9

TNM, tumour node metastasis; UICC, Union Internacional Contra la Cancrum

curative resection (41 *versus* 47 per cent) was not significant ($t = 0·43$, 1 d.f., $P = 0·51$).

It was investigated whether the long-term results after emergency curative resection improved over time to such an extent that the prognosis was comparable to that after elective resection. Univariate and multivariate analysis was performed to assess emergency surgery as a significant prognostic factor (*Table 4* and *5*), which showed that tumour stage, grade and age were significant prognostic factors in both observation periods. Sex and tumour location were significant parameters of outcome in the first but not in the second observation period. Using univariate tests, timing of surgery (emergency *versus* elective) was linked to prognosis before and after 1988. However, regression analysis revealed that the timing of surgery was an independent prognostic factor only in the 1982–1987 period.

Discussion

The results of emergency surgery for colorectal cancer in this unit were poor in the early 1980s[9]. New surgical strategies were introduced by the end of the decade: one-stage resection and initial radical lymphadenectomy. This study examined their impact on outcome by comparing the results of two periods (1982–1987 and 1988–1993). Patient and tumour characteristics as well as the rate of

Table 5 Proportional risk regression models of prognostic factors with regard to overall survival for colorectal cancer following curative resection

	1982–1987 ($n = 618$)*		1988–1993 ($n = 698$)†	
	Relative hazard	*P*	Relative hazard	*P*
TNM (UICC) stage				
II *versus* I	1·33 (0·97–1·83)	<0·001	1·82 (1·19–2·78)	<0·001
III *versus* I	1·82 (1·33–2·48)		3·15 (2·09–4·74)	
IV *versus* I	4·51 (2·43–8·36)		7·52 (4·09–13·80)	
Grade				
I/II *versus* III/IV	1·53 (1·14–2·06)	0·0045	1·80 (1·33–2·42)	<0·001
Age (years)				
≤66 *versus* >66	1·79 (1·40–2·29)	<0·001	1·89 (1·42–2·49)	<0·001
Sex				
Male *versus* female	0·62 (0·49–0·80)	<0·001	n.a.	0·43
Surgery				
Elective *versus* emergency	2·02 (1·30–3·15)	0·0017	n.a.	0·41
Tumour site				
Colon *versus* rectum	1·33 (1·03–1·72)	0·028	n.a.	0·47

Values in parentheses are 95 per cent confidence intervals. Data for *41 and †12 patients missing. TNM, tumour node metastasis; UICC, Union Internacional Contra la Cancrum; n.a., not applicable

emergency surgery were comparable for both periods. The incidence of emergency operation of about 8 per cent is much lower than many others in the literature[1,2,11–13]. This discrepancy may be explained by the fact that only true abdominal emergencies, i.e. operations within 24 h of admission, were studied whereas other reports included patients with urgent or delayed surgery in their analysis or defined emergency patients by their admission mode rather than by the timing of surgery[14].

The important finding of this study is improved postoperative and long-term outcome over time. The overall hospital mortality rate declined significantly from 18 per cent to 4 per cent after 1988. Imminent death from obstruction or perforation (14 and 30 per cent) was no longer a threat after 1988 (4 and 5 per cent). These results are in the lower range of published data. Although many patients die from progressive disease soon after discharge from hospital, long-term prognosis at 3 years after curative emergency resection increased significantly with time (74 *versus* 50 per cent). The increase in 5-year survival rate (47 *versus* 41 per cent) was not significant because of the small number of survivors. The timing of operation, emergency *versus* elective, lost its prognostic significance after 1988.

The type of surgery had an immense impact on this improved outcome, since the number of fatal postoperative complications such as anastomotic leaks and persistent peritonitis were reduced in the second observation period. This improvement was not achieved by minimizing surgical procedures but by performing more aggressive emergency surgery and increasingly replacing decompression procedures with primary resection after 1988. Fatal cardiac decompensation was a typical complication of persisting ileus after decompression procedures but has nearly disappeared since this type of surgery has been abandoned. The idea that primary caecostomy or colostomy is a safe initial option seems to be a misconception, since old and frail patients fare better with resection.

The present data also support the notion that single-stage resections with primary anastomoses have no adverse effect[4]. Although primary ileocolonic anastomoses have long been considered safe colocolonic anastomoses are still regarded as hazardous after acute obstruction. Several techniques have been developed to increase the safety of primary colocolonic anastomoses including intraoperative antegrade colonic irrigation with leakage rates of 0–14 per cent[15–18] and a mortality rate of about 10 per cent[16,17,19]. Extensive resection with ileocolonic or ileorectal anastomosis is another one-stage technique avoiding initial colocolonic anastomosis. The leakage rate is less than 5 per cent[20–22]. The SCOTIA (subtotal colectomy *versus* on-table irrigation and anastomosis) study group performed the first prospective randomized trial to compare subtotal colectomy with segmental resection and primary anastomosis following intraoperative irrigation for the management of malignant left-sided colonic obstruction[23]. Postoperative morbidity was somewhat higher in the subtotal colectomy group, but this difference was not significant. The hospital mortality rate was similar in the two groups: late bowel problems, increased bowel frequency and a higher stoma rate were significantly more common in the subtotal colectomy group. The SCOTIA study group concluded that segmental resection following intraoperative irrigation was the preferred option except in cases of perforation of the caecum, when subtotal colectomy was more appropriate.

The outcome of tumour perforation also improved without an obvious change in surgical strategy. Primary resection and eradication of the septic focus were standard in both observation periods. This became a generally accepted strategy after many studies reported a decrease in mortality rate from about 50 per cent after staged resection to less than 30 per cent after primary resection. With regard to earlier reports of extremely high anastomotic leakage rates, most authors still agree that peritonitis precludes primary anastomosis and, thus, recommend Hartmann's discontinuity resection as the standard procedure for perforating tumours of the left colon[8]. Persistent peritonitis and sepsis were frequent complications and the main cause of death in the present patients in the early 1980s. In the late 1980s, however, the fatal risk of sepsis decreased; in fact, most patients survived the emergency situation suggesting that superior intensive care management most likely contributed to the success.

Patients with obstructing or perforated colorectal cancer are known to have a significantly reduced long-term survival compared with patients undergoing elective surgery[24–26] even when analysed stage by stage[27]. The increase in radical lymphadenectomies with time from 13 per cent (six of 46) to 61 per cent after 1988 was associated with significantly improved long-term survival at 3 years from 50 to 74 per cent. Because of the small number of patients, the survival advantage was not significant at 5 years. The prognostic relevance of the timing of surgery was then further analysed by multiple regression analysis. This clearly showed that emergency surgery was an independent factor between 1982 and 1987 ($P = 0{\cdot}0017$) but not between 1988 and 1993 ($P = 0{\cdot}41$). This suggests that the long-term prognosis of emergency patients improved to such an extent that it became comparable to that of elective patients with a similar risk profile. These data support the concept that radical resection techniques have a positive impact on long-term prognosis of emergency colorectal cancer.

In summary, these results demonstrate some progress in the management of obstructing or perforating colorectal cancer. Although there is still about a 5 per cent postoperative mortality rate among these frail patients, overwhelming septic abdominal complications were almost eliminated as a major cause of morbidity and death. With better management of the emergency situation, more attention can be given to the underlying oncological problem. Long-term prognosis may become independent of the timing of surgery (elective *versus* emergency) if radical resection is performed. Thus, systemic lymphadenectomy should probably be performed in more patients to improve long-term survival.

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Short note

Early experience with day-case transthoracic endoscopic sympathectomy

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Transthoracic endoscopic sympathectomy is an effective treatment for palmar hyperhidrosis[1]. Most operations are conducted on inpatients, often with discharge the day after surgery. This study reports a series of patients in whom the procedure has been performed in the day-surgery unit.

Patients and methods

Over 20 months, 20 transthoracic endoscopic sympathectomies were performed in 13 patients. All patients had severe, long-standing, bilateral palmar hyperhidrosis. They had a mean age of 22 (range 16–33) years and seven were women. All were American Society of Anesthesiologists grade I. After a preadmission visit, the patients were admitted directly to the day-surgery unit where all procedures were performed on a morning operating list by the senior author. In each case, a unilateral procedure was performed, commencing on the side of the dominant hand. The patients were reviewed by both the consultant surgeon and consultant anaesthetist during the afternoon following surgery and, if fit for discharge, were allowed home before the day-surgery unit closed at 18.00 hours.

A standard surgical technique was used[2] but without carbon dioxide insufflation. Analgesia was provided by intravenous morphine, diclofenac suppositories and intrapleural bupivacaine. The patients also routinely received an H_2-receptor-antagonist and an antiemetic.

Results

The mean duration of the 20 procedures was 41(range 20–60) min. Eighteen were successfully completed as a day case. Two patients required overnight admission: during one procedure there was a brief period of bleeding from a trocar site which settled with direct external pressure and one patient had a temporary fall in oxygen saturation (to 92 per cent) in the recovery room. The chest radiograph of the second patient, a cigarette smoker, showed an area of atelectasis and she was treated with physiotherapy. Both patients were discharged the following morning.

Eleven of the 13 patients, who had between them a total of 17 procedures, responded to a questionnaire. All described a significant and immediate improvement in symptoms following surgery. Compensatory sweating developed after 11 operations, mostly around the trunk, but one patient described facial gustatory sweating. Two patients have noticed a slight recurrence of their symptoms at 8 and 14 months following sympathectomy.

The majority of patients (nine of 11) complained of both nausea and intrathoracic pain in the first 24 h after surgery. Despite this, all were satisfied with their treatment and their management as a day case. Three patients would have preferred inpatient care for pain control.

Discussion

This paper describes 20 transthoracic endoscopic sympathectomies planned as day-case operations, with overnight admission required after two procedures and good levels of patient satisfaction. Conducting the operation on an outpatient basis does not appear to affect the efficacy of the procedure; the problems of compensatory sweating and late recurrence are comparable to those of other inpatient series[1,3,4].

It was decided to operate on only one side at a time to limit perioperative complications and perhaps also reduce the incidence of compensatory sweating. Six of the patients were satisfied with the results of the unilateral procedure and declined surgery to the other hand. Carbon dioxide insufflation appears to be unnecessary and has been reported to cause severe hypotension and bradycardia[5] with a potentially fatal mediastinal shift if introduced too rapidly.

The problems of pain and postoperative nausea and vomiting remain unresolved. Current measures provide acceptable analgesia in the first 6 h after operation but clearly therapy could be improved after the patient returns home.

These early results suggest that with improved postoperative analgesia transthoracic endoscopic sympathectomy may be performed effectively as a day case.

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Malignant epithelial parotid gland tumours: analysis and results in 65 previously untreated patients

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Background Optimal management of malignant epithelial parotid tumours requires knowledge of the available therapeutic modalities and the different biological characteristics. The aim of the study was to review the characteristics of patients at presentation, histological classification, disease-free and overall survival rates, and the results of the applied treatment policy regarding the facial nerve and neck.

Methods Between 1974 and 1995 a total of 65 patients was treated with curative intent for a previously untreated malignant epithelial parotid gland tumour. All patients underwent some type of parotidectomy, 20 of whom had an *en bloc* radical neck dissection. In selected cases the facial nerve or its branches were peeled off the tumour thus violating the objective of tumour-free margins and relying heavily on the efficacy of postoperative radiotherapy. In total 51 patients received postoperative radiotherapy. None of the patients was lost to follow-up.

Results There were 12 locoregional failures (18 per cent). In only one of these 12 patients was salvage therapy successful; the remaining 11 patients died from the tumour. All but one of the eight patients with distant metastasis only died from the tumour. The estimated 5- and 10-year disease-free rates were 68 and 59 per cent respectively. The corresponding survival rates were 75 per cent and 67 per cent. A significant relationship could be observed between tumour stage and survival. The presence of lymph node metastases proved to be the strongest single prognostic factor.

Conclusion In selected cases a conservative approach towards the facial nerve is justified.

Salivary gland neoplasms account for 3 per cent of all tumours in the head and neck region[1]. Approximately 75–85 per cent of these neoplasms occur in the parotid gland, of which 20–25 per cent are malignant[2,3]. Their behaviour varies according to the histopathological subtype[4,5].

Approximately 50 per cent of malignant parotid gland neoplasms present as an asymptomatic, slowly growing, firm elastic swelling, freely mobile under the skin at or near the angle of the mandible or in front of the ear, and usually there are no obvious features to differentiate these from benign parotid neoplasms[6]. The remaining group of patients shows signs consistent with malignant disease such as facial nerve dysfunction, suspicious lymph nodes in the neck, trismus, or fixation of the tumour to the skin and/or the underlying tissues. Pain is suspicious for malignancy[7].

Diagnostic imaging studies are rarely required in patients who present with a typical asymptomatic mass. If, however, assessment of the extent of disease is required this should be performed preferably using magnetic resonance imaging (MRI)[8]. Preoperative fine-needle aspiration cytology (FNAC) is advocated by some authors[9–11].

Surgery is the primary treatment for malignant tumours of the parotid gland while postoperative radiotherapy has been proven to be effective as an adjunct to surgery in improving local control and survival[12–15]. Additionally, radiotherapy is applicable as a treatment modality for inoperable tumours, or in patients who are unfit for surgery[16].

Optimal management of these rare tumours requires knowledge not only of the available therapeutic modalities but also of the different biological characteristics of this heterogeneous group of tumours.

This study reviews the characteristics of patients at presentation, histological classification, and disease-free and overall survival rates between 1974 and 1995. Additionally, it evaluates the results of a treatment policy regarding the facial nerve and the neck.

Patients and methods

Patients

From 1974 until 1995, 81 patients were treated for a malignant epithelial parotid gland tumour, of which 16 were recurrences after previous treatment elsewhere. These were excluded from the study. There were 28 women and 37 men; their ages ranged from 11 to 92 (median 59) years. The peak incidence occurred in the eighth decade.

For patients treated from 1974 to 1990 the 1972 World Health Organization (WHO) classification for salivary gland tumours was used[4]. For patients treated after 1990 the WHO classification of 1991[5] was applied. For practical reasons the patients are presented as one group. Clinical classification as well as stage grouping were performed retrospectively using the 1992 Union Internacional Contra la Cancrum (UICC) TNM classification[17]. The T classification and the stage grouping according to the UICC are presented in *Tables 1* and *2* respectively. The division of the total group of 65 patients according to histological type and stage is presented in *Table 3*.

Thirty-two patients (49 per cent) presented with an asymptomatic mass, of whom 14 had a history of more than

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Table 1 1992 Union Internacional Contra la Cancrum tumour node metastasis clinical classification

T	Primary tumour
T_X	Primary tumour cannot be assessed
T_0	No evidence of primary tumour
T_1	Tumour 2 cm or less in greatest dimension
T_2	Tumour more than 2 cm but not more than 4 cm in greatest dimension
T_3	Tumour more than 4 cm but not more than 6 cm in greatest dimension
T_4	Tumour more than 6 cm in greatest dimension

All categories are subdivided into (a) no local extension and (b) local extension. Local extension is clinical or macroscopic evidence of invasion of skin, soft tissue, bone or nerve. Microscopic evidence alone is not local extension for classification purposes

Table 2 Stage grouping according to 1992 Union Internacional Contra la Cancrum tumour node metastasis clinical classification

Stage I	T_{1a}	N_0	M_0
	T_{2a}	N_0	M_0
Stage II	T_{1b}	N_0	M_0
	T_{2b}	N_0	M_0
	T_{3a}	N_0	M_0
Stage III	T_{3b}	N_0	M_0
	T_{4a}	N_0	M_0
	Any T (except T_{4b})	N_1	M_0
Stage IV	T_{4b}	Any N	M_0
	Any T	N_2, N_3	M_0
	Any T	Any N	M_1

Table 3 Patient distribution (1974–1994) according to histological diagnosis and tumour stage

		Tumour stage			
Histological diagnosis	Total	I	II	III	IV
Acinic cell carcinoma	12	8	3	1	0
Mucoepidermoid carcinoma	6	2	2	2	0
Adenoid cystic carcinoma	13	7	1	4	1
Myoepithelial cell carcinoma	1	1	0	0	0
Oncocytic carcinoma	1	1	0	0	0
Adenocarcinoma	17	3	7	3	4
Carcinoma in pleomorphic adenoma	6	2	3	1	0
Squamous cell carcinoma	1	0	0	0	1
Undifferentiated carcinoma	6	0	1	3	2
Carcinoma not otherwise specifiable	2	0	1	0	1
Total	65	24	18	14	9

1 year duration (median 3·0 years). Facial nerve paresis/paralysis and pain were the exclusive complaint in five and 17 patients respectively while in 11 further cases pain was accompanied by facial nerve dysfunction. Facial nerve paresis/paralysis was thus present in 16 (25 per cent) of the 65 patients, ten of whom had complete facial nerve paralysis and six a paresis of one of the major branches. In eight of the 16 patients this related to an adenocarcinoma, confirming the finding that facial nerve dysfunction is more common in adenocarcinoma than in other cancers. Seven of these patients were initially under the surveillance of the referring physician as the facial nerve dysfunction was attributed to a Bell's palsy.

In each patient FNAC was performed. In the early period of the study computed tomography was performed in patients with clinically suspicious malignant disease. In the later period these patients were evaluated radiologically by MRI.

Long-term follow-up was pursued either by clinical attendance, generally for at least 10 years, or by an enquiry to the general practitioner for patients who were dismissed from outpatient review. None of the patients was lost to follow-up.

Treatment

All patients were treated surgically with curative intent. Patients with an asymptomatic lump ($n = 32$) underwent some form of (partial) parotidectomy with preservation of the facial nerve while in the remaining group of patients ($n = 33$) who presented with clinical evidence of malignant disease a total parotidectomy was performed. An *en bloc* radical neck dissection was performed in 20 patients.

In ten patients a radical neck dissection was planned before operation as clinically positive lymph nodes were present. Furthermore, frozen-section analysis of one or more subdigastric lymph nodes was performed during surgery in all patients who presented with clinical evidence of a malignant tumour as well as in all those with an asymptomatic mass in the parotid in whom FNAC revealed malignant disease. In six of these patients frozen-section analysis revealed malignant tumour and so neck dissection was performed. In another four patients elective *en bloc* neck dissection was performed as the risk of occult lymph node metastases was considered to be high on the basis of cytological findings (e.g. high-grade tumour) or because of extent of the primary tumour into the neck.

Radical excision at a clinical and gross examination level has been obtained in all cases. Radicality at histopathological examination was defined as tumour-free margins of at least 5 mm. In the presence of tumour less than 5 mm from the margin, which is often unavoidable when preserving the facial nerve, the radicality of the excision was regarded as questionable.

In general, in each patient with facial nerve impairment the involved part of the nerve was sacrificed. In 16 patients preoperative facial nerve dysfunction was observed. In 11 of these the facial nerve was completely sacrificed while in two patients a segmental facial nerve transection was performed as in these 13 patients the tumour either encompassed the entire nerve or one of its related branches. In another three patients the nerve was preserved.

In an additional six patients acinic cell carcinoma ($n = 1$), mucoepidermoid carcinoma ($n = 2$), adenocarcinoma ($n = 1$), undifferentiated carcinoma ($n = 2$), in whom facial nerve function was normal before operation, it was decided to perform a complete ($n = 1$) or segmental ($n = 5$) facial nerve transection as the nerve or one of its main branches was completely encompassed by tumour.

Altogether in three of 12 patients who underwent transection of the main stem of the nerve an attempt to reconstruct the nerve was performed. In the other nine patients reconstruction was precluded because of perineural tumour spread or because of disease advancing up to the stylomastoid foramen. In one patient a nerve graft of the cervical plexus was used. In another patient reconstruction was performed using a nerve graft from the greater auricular nerve while in the third patient the facial nerve itself was reanastomosed on its proximal end.

Fifty-one patients received postoperative external beam radiotherapy beginning 5–7 weeks after surgical treatment (mean dose 6350 (range 4000–7000) cGy), using megavoltage methods (electron, photon or combination) administered in 4–7 weeks by one fraction per day, 5 days/week. One of the patients received after 6480 cGy an additional 2035 cGy using a radium implant. The irradiated fields were individually designed to incorporate primary tumour and neck, and the areas of potential perineural and perivascular spread. The indications for postoperative radiotherapy included histological type, questionable radicality at histological examination, perineural and/or perivascular tumour spread, and lymph node metastases.

Statistical analysis

Disease-free and survival curves were estimated using Kaplan–Meier estimators, also known as product–limit estimators. These estimators make use of the information on all patients, including those whose observations are censored. The curves were compared using the Mantel Cox test. For all curves, time of event is time following the initial surgical treatment.

For the disease-free curves, the event 'recurrence' was defined as having developed recurrent locoregional and/or distant metastatic disease. Observations were regarded as censored when the patient was free from recurrent disease at the last outpatient clinic attendance or when the patient died free from recurrent disease.

For the survival curves, the event 'death' was defined as death due to recurrent locoregional and/or distant metastatic disease. The data of a patient were regarded censored when the patient was alive at the last outpatient clinic attendance or when the patient died from natural causes or other diseases, including other tumours.

Lymph node metastasis, facial nerve dysfunction and age at diagnosis were examined as predictors for survival using Cox proportional hazards model stratified by tumour stage.

Results

In the total series of 65 patients 20 experienced locoregional recurrence or distant metastases (*Table 4*).

Locoregional recurrence

Twelve patients (18 per cent) developed a locoregional recurrence, none of whom had stage I disease (*Table 5*). The type of surgical procedure in these patients included a 'partial' ($n = 3$) or total ($n = 9$) parotidectomy.

An *en bloc* radical neck dissection was performed in seven patients because of clinical evidence of lymph node metastases ($n = 4$) or tumour on frozen-section analysis of subdigastric lymph nodes ($n = 3$). In four of these 12 patients complete facial nerve paralysis was observed before operation. In all four patients the facial nerve was sacrificed. In one of them an attempt was undertaken to reconstruct the facial nerve using a graft from the greater auricular nerve. Unfortunately, no functional recovery was observed. In the other three patients nerve reconstruction was precluded by perineural spread or disease progressing up to the stylomastoid foramen. In an additional two patients with an intact facial nerve function it was decided to perform a segmental facial nerve resection as the tumour encompassed individual branches.

Table 4 Incidence of locoregional recurrent disease and/or distant metastases related to tumour stage

	Recurrent disease		
Stage	No	Yes	Total
I	23	1	24
II	12	6	18
III	8	6	14
IV	2	7	9
Total	45	20	65

All these 12 patients, except two who refused, received postoperative radiotherapy; in another patient serious delay occurred (more than 3 months) before the start of radiotherapy because of general complications.

Four patients with recurrent locoregional tumour received further surgical treatment, which was successful in one patient. This patient died from unrelated disease without evidence of recurrent tumour after 51 months. All other patients died with disease.

Distant metastasis

Distant failure alone occurred in another eight patients, the majority of whom had stage III/IV disease (*Table 6*). The type of surgical procedures in these patients included a 'partial' ($n = 1$) or total ($n = 7$) parotidectomy.

In four patients an *en bloc* radical neck dissection was carried out because of clinical evidence of lymph node metastases ($n = 1$), malignant disease on frozen-section analysis of subdigastric lymph nodes ($n = 1$), disease extending into the neck ($n = 1$), and the finding of a squamous cell carcinoma on frozen-section analysis of the primary tumour ($n = 1$).

In three of these eight patients, facial nerve paralysis was observed before operation. In each of them it was decided to sacrifice the facial nerve. Facial nerve reconstruction was performed in two of these patients. In the third patient reconstruction was precluded by perineural tumour spread. One patient regained almost complete facial function while in the other no functional recovery was observed.

All eight patients received postoperative radiotherapy. All of them, except one who has been followed for only 29 months, died from distant metastases.

Tumour control

Tumour control was achieved in 45 patients. The surgical procedures for these patients included a 'partial' ($n = 29$) or total ($n = 16$) parotidectomy.

In nine patients an *en bloc* radical neck dissection was performed because of clinical evidence of lymph node metastases ($n = 5$) or malignant disease on frozen-section analysis of subdigastric lymph nodes ($n = 2$), while in

Table 5 Locoregional failure related to tumour stage and histopathological findings

Tumour stage		No. of patients	Failure	Histology
I	$T_{1a}N_0$	0		
	$T_{2a}N_0$	0	0 of 24	
II	$T_{1b}N_0$	0		
	$T_{2b}N_0$	3		Carcinoma in pleomorphic adenoma (two), adenocarcinoma
	$T_{3a}N_0$	1	4 of 18	Undifferentiated carcinoma
III	$T_{3b}N_0$	2		Undifferentiated carcinoma, adenocarcinoma
	$T_{4a}N_0$	1		Adenoid cystic carcinoma
	Any TN_1	0	3 of 14	
IV	T_{4b} Any N	2		Adenocarcinoma, adenoid cystic carcinoma
	Any T N_2, N_3	3	5 of 9	Squamous cell carcinoma, carcinoma not otherwise specifiable, adenocarcinoma

Table 6 Distant metastatic disease without locoregional failure, related to tumour stage and histopathological findings

Tumour stage		No. of patients	Failure	Histology
I	$T_{1a}N_0$	0		
	$T_{2a}N_0$	1	1 of 24	Carcinoma in pleomorphic adenoma
II	$T_{1b}N_0$	0		
	$T_{2b}N_0$	2		Adenocarcinoma (two)
	$T_{3a}N_0$	0	2 of 14	
III	$T_{3b}N_0$	2		Carcinoma in pleomorphic adenoma, adenoid cystic carcinoma
	$T_{4a}N_0$	0		
	Any T N_1	1	3 of 11	Mucoepidermoid carcinoma
IV	T_{4b} Any N	1		Undifferentiated carcinoma
	Any T N_2, N_3	1	2 of 4	Adenocarcinoma

another two this was carried out because the primary tumour extended into the neck and was high grade.

In five patients, four of whom had facial nerve dysfunction, it was decided to sacrifice the facial nerve. In none of these patients was facial nerve reconstruction performed. In another five patients, three of whom had normal facial nerve function before operation, a segmental resection was performed. In another ten patients, all of whom had normal preoperative facial nerve function, an intimate relation was observed between the main stem of the nerve ($n = 1$) or one of its major branches ($n = 9$) and the tumour during surgery. In all these cases (adenocarcinoma ($n = 1$), adenoid cystic carcinoma ($n = 6$) and mucoepidermoid carcinoma ($n = 3$)), the nerve could be peeled from the tumour. All of these patients received a full course of postoperative radiotherapy. None developed recurrent locoregional disease and in each patient facial nerve function remained completely intact; the median follow-up for these ten patients was 68 months.

None of the 45 patients, of whom 33 received postoperative radiotherapy, developed recurrent tumour. Ten patients died during follow-up at varying intervals from unrelated disease. Of the entire group of 65 patients, 36 patients are alive at a median follow-up of 90 months.

Facial nerve involvement

Eight of the 16 patients with preoperative facial nerve dysfunction died from locoregional or distant metastatic disease, the median survival time being 38 months. Forty-nine patients had symmetrical facial nerve function. In six of these patients either a complete ($n = 1$) or segmental ($n = 5$) facial nerve transection was performed as the nerve or one of its main branches was completely encompassed by tumour. In the remaining 43 patients the facial nerve was preserved. In 41 of these patients symmetrical facial nerve function was observed 6 months after operation. In the remaining two patients no functional recovery of the facial nerve was noted. One of these patients developed locoregional recurrence within 1 year; histopathological examination of the tumour revealed a radically excised adenocarcinoma with eight lymph nodes in the neck dissection specimen.

Histology

No patient treated for an acinic cell carcinoma ($n = 12$) developed recurrent or metastatic disease during a median follow-up of 95 months. Of the six patients treated for a mucoepidermoid carcinoma only one patient died from distant metastatic disease, the median follow-up being 85 months. Three of 13 patients treated for an adenoid cystic carcinoma died from disease; the median follow-up for the remaining nine patients was 95 months. Six of 17 patients treated for adenocarcinoma died from locoregional and/or metastatic disease. Another four of these patients died from unrelated disease. At present seven patients are alive at a median follow-up of 96 months, one of whom has distant metastatic disease only. Six patients were treated for carcinoma in a pleomorphic adenoma. Four of these patients died from disease, three within 3 years. Three of six patients treated for an undifferentiated carcinoma died from the tumour.

In 15 patients radicality was confirmed at histological examination. In the remaining 50 patients tumour cells were present at a distance less than 5 mm from the surgical margins, occasionally even extending into the margin.

Twenty patients underwent *en bloc* neck dissection. In 17 of these specimens lymph node metastases were demonstrated. This related to the following histology: adenocarcinoma (eight of 17), undifferentiated carcinoma (three of six), squamous cell carcinoma (one of one), carcinoma not otherwise specifiable (one of two), carcinoma in pleomorphic adenoma (one of six), mucoepidermoid carcinoma (one of six), acinic cell carcinoma (one of 12), and adenoid cystic carcinoma (one of 13).

Survival

The disease-free and corresponding survival curves for the entire group of patients are presented in *Fig. 1*. The estimated 5- and 10-year disease-free rates were 68 and 59 per cent. The corresponding survival rates were 75 and 67 per cent respectively.

Using the Kaplan–Meier estimators a significant relation could be observed between tumour stage and decreasing disease-free and overall survival rates ($P < 0{\cdot}001$). The disease-free and survival curves related to tumour stage are shown in *Figs 2* and *3*.

The only significant prognostic variable in the Cox proportional hazards model, stratified by tumour stage, was the presence of lymph node metastases.

Discussion

Studies of epithelial parotid gland tumours are difficult to compare as different authors have used different

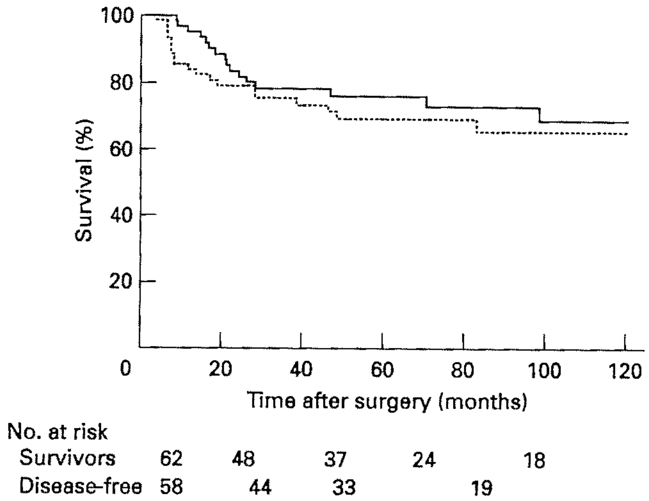

Fig. 1 Disease-free (– – –) and overall (——) survival curves for the entire group of patients

classification systems and different ways of reporting the results. The 5- and 10-year survival rates in this series of 75 and 67 per cent are comparable with the best recently published results[18–20].

As reported in other studies the clinical stage, particularly lymph node metastasis and preoperative facial nerve involvement, as well as the histopathological type, were paramount factors strongly influencing the incidence of recurrence and survival rates[4,18–22]. None of the patients with a T_1 tumour experienced recurrent disease while 13 of 20 patients who developed recurrent disease were treated for a T_3 tumour and/or lymph node metastases of the neck.

Tumour histology had a significant influence on survival. In this study, as reported by others, survival rates were highest for patients with acinic cell carcinomas, mucoepidermoid carcinomas and adenoid cystic carcinomas[23]. The poorest survival was observed in patients with an adenocarcinoma, carcinoma in a pleomorphic adenoma and undifferentiated carcinoma.

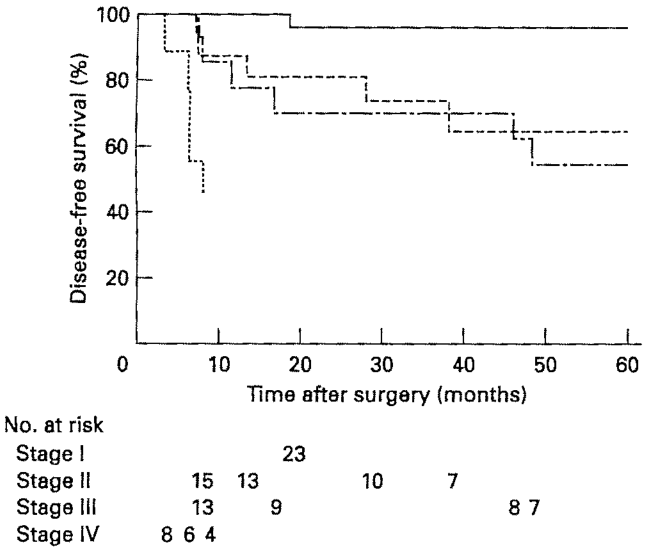

Fig. 2 Disease-free survival curves related to tumour stage. (——), Stage I; (– – –), stage II; (—·—·—), stage III; (....), stage IV

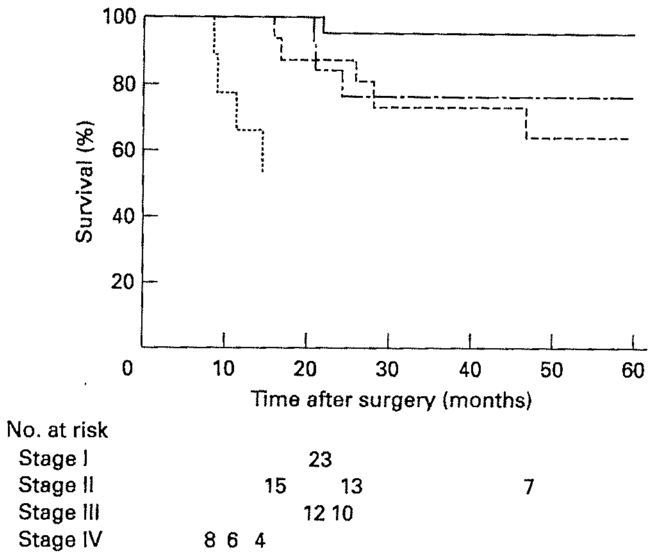

Fig. 3 Overall survival curves related to tumour stage. (——), Stage I; (– – –), stage II; (—·—·—), stage III; (....), stage IV

The incidence of manifest cervical lymph node metastasis ($n = 10$; 15 per cent) was similar to that reported by others[24,25]. Moreover lymph node metastases were demonstrated during surgery in another six patients with an asymptomatic tumour on frozen-section examination of subdigastric lymph node(s). This emphasizes the importance of peroperative lymph node sampling and immediate frozen-section analysis.

Histological cell type appears to be related to the risk of lymph node metastases. In this series adenocarcinoma and undifferentiated carcinoma in particular were associated with a high incidence of lymph node metastases; in contrast lymph node metastases were rare in adenoid cystic carcinoma and in acinic cell carcinoma. In the literature it is reported that squamous cell carcinoma and mucoepidermoid carcinoma also carry a high risk for lymph node metastases[3,26]. Histopathological examination revealed lymph node metastases in 17 of 20 neck dissections. Ten of these 17 patients died from locoregional and/or metastatic disease; the median survival time of these ten patients was 24 months. The remaining 45 patients underwent resection of the tumour alone. Of this group, six patients died from locoregional or distant metastatic disease; the median survival time for these six patients was 64 months. These findings confirm the poor prognosis if lymph node metastases are present and stress again the significance of instantaneous frozen-section analysis of subdigastric lymph nodes in the event of a parotid gland carcinoma.

The incidence of facial nerve palsy due to tumour infiltration was similar to that reported by others[27]. Facial nerve involvement before treatment is more common in high-grade tumours and is associated with a worse prognosis. Indeed, eight of 16 cases related to an adenocarcinoma. Eight of the 16 patients died from locoregional and/or metastatic disease, the median survival time being 38 months, thus supporting the bad prognosis.

One of the most difficult problems that can occur during surgery is when the tumour lies very close to a facial nerve whose function was intact before operation. The two objectives of parotid surgery, i.e. removal of the tumour and preservation of the facial nerve, are then in conflict. This treatment dilemma was encountered in 16 patients. The surgical philosophy in such cases is conservative. However, if the facial nerve is surrounded by tumour, as in six of these patients, and preservation of the nerve would leave macroscopic remnants of tumour, the nerve should be resected with a healthy margin. Usually this requires resection of the main trunk and its primary branches. In such cases immediate microsurgical reconstruction of the continuity of the nerve is carried out using a graft, provided that the size of the defect and the age of the patient provide a reasonable chance of success of such a procedure. However, if the tumour extends close to the nerve, as was the case in ten patients, the facial nerve is carefully peeled off the tumour although this transgresses the classical oncological principle that malignant tumours should be removed with a wide healthy margin. After a full course of postoperative radiotherapy none of these ten patients, with a median follow-up of 68 months, developed locoregional recurrence and in each patient facial nerve function remained completely intact. Furthermore, the facial nerve was preserved in three patients with preoperative facial nerve dysfunction of a total of 16 patients. None of these three patients developed a locoregional recurrence, and facial nerve function recovered completely in two of the three. These results support a conservative approach with regard to the facial nerve in selected cases, and confirm the efficacy of postoperative radiotherapy in eradicating microscopic remnants of tumour after surgery.

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Detection of residual disease following breast-conserving surgery

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Background Assessment of completeness of tumour excision has become an integral part of breast-conserving surgery, but the accuracy of margin analysis has been questioned. This study compared the results of resection margin analysis with an examination of tumour bed biopsies and of the excised cavity wall.

Methods One hundred and forty-four patients underwent breast-conserving surgery for T_{1-2} N_{0-1} breast cancer. Following wide local excision, four bed biopsies were taken from the cavity wall which was then completely excised. The presence of invasive and *in situ* disease at the inked resection margin (IRM) and in the adjacent bed biopsies and cavity wall was recorded.

Results Positive margins and/or residual disease in either the bed biopsies or cavity wall was found in 62 (43 per cent) of 144 cases. Residual disease (invasive or *in situ*) was present at the IRM in 39 specimens (27 per cent) and was present in 25 bed biopsy (17 per cent) and 39 cavity wall (27 per cent) specimens. These comprised different but overlapping groups of patients.

Conclusion Margin analysis of wide local excision specimens is a poor predictor of completeness of excision. Routine resection and examination of the entire cavity wall increases the detection of residual disease compared with examination of bed biopsies alone and is a useful adjuvant to conventional margin evaluation.

Breast-conserving surgery is the preferred treatment for most early breast cancers and low rates of local recurrence can be achieved with a good cosmetic outcome[1]. Local recurrence increases with length of follow-up, with rates of up to 35 per cent following lumpectomy without adjuvant radiotherapy[2,3] and up to 22 per cent with radiotherapy[4,5]. A number of risk factors are associated with an increased likelihood of local recurrence[6,7], including the presence of disease at the IRM, indicating incomplete excision. The clinical significance of a positive IRM remains unclear[8–12], as up to a third of patients with involved margins have no identifiable residual disease on subsequent examination of the mastectomy specimen[13]. Conversely, a negative margin may underpredict residual disease, as demonstrated by the reanalysis of the National Surgical Adjuvant Breast and Bowel Project, Protocol B06 trial, in which recurrence rates of 35 per cent were observed in patients with negative margins treated by lumpectomy alone[2].

A number of techniques have been developed alongside margin analysis in an attempt to increase the detection of residual disease after breast-conserving surgery. These include re-excision of positive margins, and examination of bed biopsies of the cavity[1,6,14,15] or cavity shavings without inked margin assessment[16].

This study compared pathological evaluation of the IRM, bed biopsies and the completely excised cavity wall to determine their relative value in establishing the adequacy of surgical excision.

Patients and methods

Patients with T_{1-2} N_{0-1} carcinomas confirmed by triple assessment were entered prospectively into the study, between 1991 and 1995. They either presented with symptoms or through the National Breast Screening Programme. Informed consent was obtained in all cases.

Patients underwent a standard wide local excision and a level I axillary dissection. The tumour was excised with a 2-cm lateral margin of palpably normal tissue and a deep margin which included the pectoral fascia. Following excision of the primary tumour, four bed biopsies were taken from the superior, inferior, medial and lateral walls of the cavity. The entire cavity wall was then re-excised, producing a specimen shaped like a ring doughnut (*Fig. 1*). The thickness of the excised cavity wall was approximately 1 cm, depending on the position of the tumour and the size of the breast. All operations were performed by the same surgeon (R.M.R.).

The wide local excision and cavity wall specimens were weighed and the former specimen was 'inked' with alcian blue.

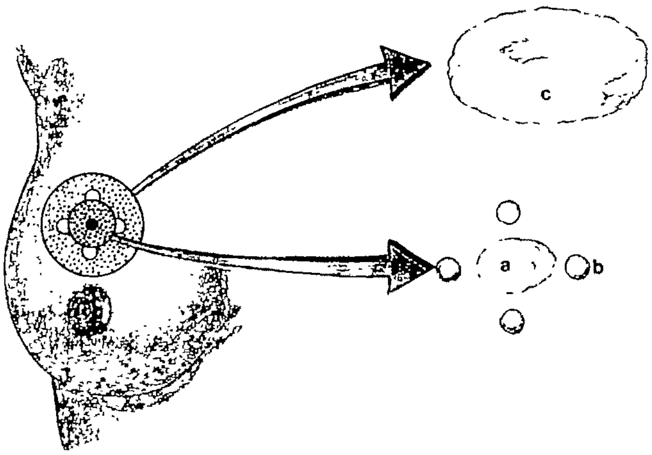

Fig. 1 Tissue excised during breast-conserving surgery for cancer. a Wide local excision, b bed biopsies and c excised cavity wall

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The maximum diameter of the wide local excision specimen and the tumour was recorded together with the tumour type, grade and presence of extensive *in situ* carcinoma, defined as an intraduct component which constituted 25 per cent or more of the whole tumour and extended into the surrounding breast tissue[17]. For analysis, the wide local excision specimen was sliced transversely, like a loaf, to establish the exact location of the tumour. Three to four blocks were taken, containing tumour and the nearest resection margin. One section was taken, at a single level, from each tissue block. The resection margin was scored positive when invasive or *in situ* tumour was identified at the inked surface of the wide local excision specimen. The cavity wall specimen was sectioned radially for naked-eye identification of fibrous areas. The fibrous areas were completely blocked out, producing anything from five to 30 blocks. The number of blocks depended on whether the cavity wall specimen was predominantly fatty or fibrous. Between one and two blocks were taken from the bed biopsies depending on their size. The bed biopsy blocks were step sectioned to increase the accuracy of identification of *in situ* or invasive disease. The lymph nodes were counted and each node was examined for the presence of metastatic disease.

Statistical analysis

A comparison of the ability of the three methods to detect residual disease was assessed by McNemar's χ^2 test. The association between the detection of any residual disease (invasive or *in situ*) and patient and tumour characteristics was examined by maximum likelihood logistic regression, with a secondary analysis concentrating on the detection of residual invasive tumour and residual *in situ* disease separately. After initial univariate analysis, the data were further analysed with multivariate regression, which is explained fully in the results section. For the tumour characteristics considered, the grade was classified in the usual way (i.e. grade I, II or III). Tumour type was considered as ductal, lobular, tubular or other. Tumours with both ductal and lobular components were classified as lobular for the purpose of statistical analysis. Odds ratios for tumour type were calculated by taking a combined estimate of the odds for all non-lobular tumours as the reference (data not shown). The tumour size, cavity wall weight, and specimen size and weight were treated as continuous variables (as opposed to being arbitrarily categorized), after being log transformed to reduce any effect of influential outliers. The patient's age was also considered as a continuous variable in the analysis.

Results

One hundred and forty-four patients were entered into the study with median age of 51 (range 27–86) years. Details about the excised pathological specimens appear in *Table 1*.

Invasive and in situ *disease*

Overall, 62 patients (43 per cent) had evidence of incomplete excision of invasive or *in situ* disease, with a positive IRM or disease found in cavity wall or bed biopsy specimens. Of these, 39 (27 per cent) had a positive IRM, 39 (27 per cent) had disease detected in the cavity wall and 25 (17 per cent) had disease detected in the bed biopsies (*Fig. 2*). Nine invasive and 16 *in situ* tumours were found on bed biopsy examination, which detected significantly fewer cases of incomplete excision than examination of the IRM ($\chi^2 = 6·12$, $P = 0·013$) or of the cavity wall ($\chi^2 = 8·33$, $P = 0·004$). Although IRM and cavity wall examination detected the same number of patients with evidence of incomplete excision, there was lack of agreement in 36 (63 per cent) of 57 patients (*Fig. 2*).

Table 1 Specimen details from 144 patients undergoing conservative surgery for breast cancer

Tumour	
Diameter (mm)*	18 (5–45)
Grade	
I	30
II	68
III	46
Type	
Ductal	87
Lobular	14
Tubular	26
Medullary	8
Colloid	4
Cribriform	3
Ductal + lobular	2
Excision specimen	
Diameter (mm)*	70 (25–150)
Weight (g)*	54 (7–214)
Cavity wall	
Weight (g)*	50 (7–188)
Lymph nodes	
No. of nodes*	12 (2–31)
No. of patients with positive nodes	48

*Values are median (range)

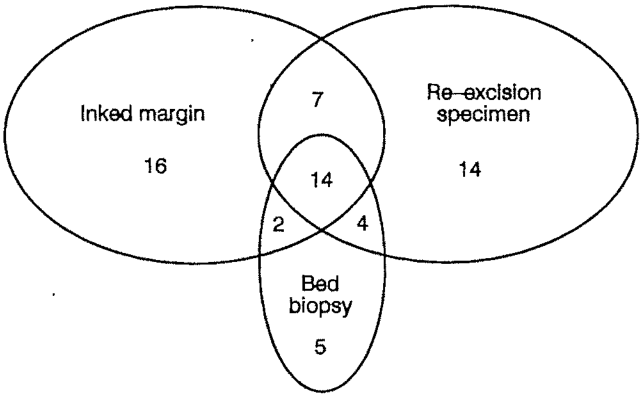

Fig. 2 Relationship between the ability of three methods to detect evidence of residual disease (invasive or *in situ*) ($n = 62$). The numbers of cases detected by each method are shown

Incomplete excision of disease (invasive or *in situ*), as judged by IRM analysis, was significantly associated with the patient's age. Older women were less likely to have a tumour detected (odds ratio 0·68 per 10-year age increase, $P = 0·04$). Patients with a lobular tumour were more likely to have residual disease detected by the bed biopsies (odds ratio 3·17, $P = 0·03$) and by examination of the cavity wall (odds ratio 4·15, $P = 0·004$). No other patient or tumour characteristic was associated with detection of residual disease. Considering a positive result from any of the three methods of detection as evidence of residual disease, no patient or tumour characteristic was strongly influential; the most important factor was the presence of a lobular tumour (odds ratio 2·22, $P = 0·10$).

Further analysis was performed on each outcome using multivariate logistic regression, with each variable analysed in turn allowing for tumour type (lobular *versus* all others) and patient age in all cases. This did not suggest any additional associations between detection of residual disease and patient and tumour characteristics.

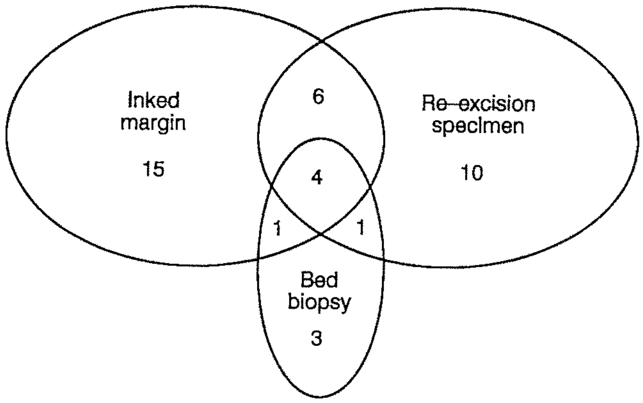

Fig. 3 Relationship between the ability of three methods to detect evidence of residual invasive disease ($n = 40$). The numbers of cases detected by each method are shown

Invasive disease

Incomplete excision of invasive carcinoma was found in 40 (28 per cent) of 144 patients. Invasive disease was identified at the IRM in 26 (18 per cent), in the cavity wall in 21 (15 per cent) and in one or more bed biopsies in nine (6 per cent). Agreement between all three techniques was found in 4 of 40 patients (*Fig. 3*). Incomplete excision of invasive disease as judged by IRM analysis was significantly associated with the patient's age (odds ratio 0·64 per 10-year age increase, $P = 0{\cdot}04$) and increasing size of the tumour (odds ratio 4·20, $P = 0{\cdot}02$). In addition, there was evidence that lobular tumours were associated with increased detection rates with both bed biopsy (odds ratio 3·47, $P = 0{\cdot}10$) and cavity wall (odds ratio 4·19, $P = 0{\cdot}01$) methods. No other factors were influential. Again, overall detection of invasive cancer was higher among lobular tumours, although not significantly.

In situ *disease*

Although tumour size was found to be positively associated with more incompletely excised invasive cancers detected by IRM analysis, it was also associated with fewer cases of residual *in situ* disease detected by analysis of IRMs (odds ratio 0·26, $P = 0{\cdot}02$). Furthermore, residual *in situ* disease was found at the IRM in five of the nine patients with extensive *in situ* carcinoma, compared with just 14 of the remaining 135 (odds ratio 10·8, $P = 0{\cdot}001$). With the relatively low rate of detection of residual *in situ* disease by bed biopsies, no strong associations were found, although there was evidence that detection was greater among patients with either extensive *in situ* carcinoma or lobular tumours. For residual disease detected by the cavity wall method, lobular tumours were again more likely to be detected (odds ratio 3·47, $P = 0{\cdot}02$), with similar detection rates among ductal, tubular or other types of tumour. No other factors were found to influence the detection of *in situ* disease.

Discussion

Combining an examination of the IRM, bed biopsies and the cavity wall following wide local excision identified a large group of patients (43 per cent) in whom the excision was either incomplete or doubtful. Moreover, the presence of tumour at the IRM was a poor predictor of residual disease. Although bed biopsy examination increased the detection of residual disease when used as an adjuvant to margin examination, analysis of the cavity wall was significantly more informative.

A 43 per cent risk of residual disease following breast conservation is not surprising, in view of the pattern of disease that has been established by careful analysis of mastectomy specimens. Using whole breast section techniques Holland *et al.*[18] detected microscopic disease 2 cm from the edge of the reference tumour in 43 per cent of mastectomies. The figure of 43 per cent in the present study almost certainly overestimates the number of patients in whom resection was truly incomplete. Although bed biopsy or cavity wall disease is clear evidence of incomplete resection, a positive IRM in association with negative bed biopsy and cavity wall specimens casts doubt on the predictive value of margin analysis in at least some of these cases.

The finding of a clear IRM in the presence of an involved cavity wall or bed biopsy is of concern but may be explained by the discontinuous growth pattern commonly seen around primary tumours[19]. Furthermore, IRM analysis is based on the examination of samples which represent a relatively small portion of the total surface area of a wide local excision specimen. By excising the entire cavity wall, the pathologist is presented with further material on which to judge the completeness of excision[20]. The finding of a clear cavity wall in patients with tumour at the IRM is more difficult to explain. While the disease may stop at the resection margin, it seems more likely that examination of representative blocks of the cavity wall fails to detect all cases of residual disease. Alternatively, a false-positive IRM may be reported as a result of the tendency for ink to track down the interstices of the specimen through defects in the surface[21], or because of damage to the surface of the specimen before inking and fixation.

Examination of the cavity wall is more likely to detect residual disease than examination of bed biopsies alone, in view of the greater amount of tissue available for scrutiny. The findings of this study reflect the limitations of bed biopsy analysis, but it is noteworthy that in seven patients disease was present in the bed biopsy, when the cavity wall was clear. In these cases disease may have been detected in the cavity wall specimen had the bed biopsies not been taken.

A number of reports have identified several variables that are associated with an increased risk of local recurrence[6–8,10,11,21]. In this study, when considering a positive result from any of the three methods of detection as evidence of incomplete excision, no overall association with the measured variables was found. However, incomplete excision of invasive disease, as judged by IRM analysis alone, was significantly associated with patient age and size of the tumour. Furthermore, there was a strong association between detection of *in situ* disease at the IRM and the presence of extensive *in situ* carcinoma. Patients were also significantly more likely to have residual disease detected in the bed biopsies or cavity wall if they had lobular tumours. These data refer to evidence of incomplete excision of disease; mature data on local recurrence are not yet available in these patients. Many studies have shown a strong association between margin positivity and local recurrence[5,6,12,19,21]. Some that failed to detect a correlation were based on incomplete data relating to margin involvement or unusually high doses of adjuvant breast irradiation[7]. As local recurrence is related to the length of follow-up and continues to occur at 1 per cent per annum after 10 years[22], further follow-up of the patients in this study will clarify the clinical value of each method (IRM, bed biopsy and cavity wall) in defining the risk of local recurrence. The increased detection of residual disease associated with cavity wall examination may lead paradoxically to a decrease in the local recurrence rate[23], because of the wider resection afforded by this technique.

This study has highlighted the limitations of using the IRM to predict the completeness of excision following wide local excision. Concurrent excision of the cavity wall leads to an increase in the detection of residual disease compared with examination of bed biopsies in isolation. Routine excision of the cavity wall at the time of wide local excision may reduce the need for further surgery when the IRM is positive or equivocal, and provides more comprehensive information on which to base decisions.

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British Journal of Surgery 1998, 85, 1277

Short note

Efficacy of cetrimide–chlorhexidine combination in surgery for hydatid cyst

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Instillation of a scolicidal agent into hepatic hydatid cysts to reduce the risk of spillage of viable protoscoleces is an integral part of the surgical technique for many surgeons[1]. Although numerous scolicidal agents have been used for many years, good evidence attesting to their efficacy *in vivo* is lacking.

In this clinical study, the efficacy of a 0·5 per cent cetrimide–0·05 per cent chlorhexidine combination (diluted Savlon, Zeneca-Abdi Ibrahim, Istanbul, Turkey), which was reported previously to be one of the most potent scolicidal agents in an *in vitro* study[2], was tested.

Patients and methods

Sixteen consecutive patients with 25 liver cysts were studied. Only type I and II cysts of Gharbi *et al.*[3] were studied, according to a fixed protocol. Multivesicular cysts were excluded.

Cysts were punctured and a maximum amount of fluid was aspirated. The viability of protoscoleces in this fluid was determined. Living protoscoleces show characteristic motility and do not take up 0·1 per cent eosin. After this step diluted Savlon solution was instilled into the cyst cavity equal to the amount of previously aspirated cyst fluid. After 5 min of exposure the cyst fluid was reaspirated and immediately evaluated for protoscolex viability. The germinative membranes were excised from the cavity and their imprints were evaluated for protoscolex viability.

Results

In 23 of 25 cysts, all protoscoleces were inactivated after 5 min of exposure. However, two cysts were found to contain viable protoscoleces although the majority of the protoscoleces were inactivated. Twenty-one of 25 germinative membrane imprints evaluated contained dead protoscoleces. In four of the germinative membranes viable protoscoleces were detected, although in two of these cysts viable protoscoleces could not be shown in the cystic fluid.

Discussion

Dissemination of protoscolex-rich fluid during surgery is a major cause of recurrence[4]. Instillation of scolicidal agent into the cyst before opening is the most commonly employed measure to prevent this serious complication. Although many surgeons regard this manoeuvre as an inseparable step, lack of objective data and complications have led some surgeons to question and abandon this routine measure[5].

Numerous scolicidal agents have been proposed in the literature without satisfactory scientific data to support their use. This lack of information led the authors to conduct this clinical study of the efficacy of a scolicidal agent. Diluted Savlon was found to be the most potent scolicidal agent in a previous *in vitro* study[2]. The results of the present study clearly demonstrate that, although it is impossible to obtain a 100 per cent scolicidal efficacy *in vivo*, very high rates of neutralization can be achieved. In conjunction with prevention of cystic fluid spillage, total evacuation and prevention of any contact of the germinative membrane with the peritoneal surface are essential because the germinative membrane can contain viable protoscoleces despite proper cyst fluid inactivation.

Walling off the surgical field with laparotomy sponges soaked in scolicidal agents is the most important step in hydatid cyst surgery. In addition this study shows that intracystic injection of diluted Savlon solution into type I and II cysts is an effective measure against the dissemination of viable protoscoleces.

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Informed consent in patients with acute abdominal pain

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Background This study aimed to establish perceptions of informed consent in patients undergoing surgery for acute abdominal conditions.

Methods A prospective observational study was carried out using a structured questionnaire-based interview technique in patients undergoing surgery for acute abdominal conditions. Main outcome measures were to establish the effects of pain and preoperative analgesia on informed consent, patient comprehension of planned surgery and the degree of discussion of potential side-effects and complications.

Results Thirty-one of 49 patients perceived that pain did not interfere with their ability to give informed consent. Forty of 48 stated that preoperative analgesia did not impair their ability to give informed consent. Forty-two understood why an operation was being planned but 28 patients stated that there had been no preoperative discussion of any potential side-effects or complications of surgery.

Conclusion In this study the majority of patients perceived that they retained the ability to give informed consent despite the effects of pain and analgesia. Although the majority of patients understood why an operation was being planned there is a clear need for improved discussion of potential side-effects and complications.

Informed consent implies that an individual understands the proposed medical treatment. He or she should understand the principal benefits, risks and alternatives, and should be able to make a free choice without pressure[1].

The nature of emergency surgery may affect an individual's ability to give informed consent. In situations requiring true emergency surgery, for example surgery for ruptured abdominal aortic aneurysm, there is little disagreement that the surgeon can act in the best interests of the patient without obtaining written consent. However, the majority of patients admitted with acute abdominal pain undergo a period of investigation and resuscitation before surgery. There is thus an opportunity for a detailed consent interview. Given the increasing awareness of a patient's need to be fully informed about any proposed procedure and the increase in medicolegal activity, often relating to lack of communication[1], it is important to establish to what extent informed consent can be obtained from patients with acute abdominal pain. Owing perhaps to an assumption that patients with acute abdominal conditions cannot give informed consent because of the effects of pain, there have been few studies in this area. This study used a questionnaire-based interview technique to establish perceptions of informed consent in patients undergoing surgery for acute abdominal conditions.

Patients and methods

Study design

This was a prospective observational study using a structured questionnaire-based interview technique to obtain a qualitative record of perceptions of informed consent in patients who have undergone surgery for acute abdominal conditions.

Questionnaire

Data were recorded in response to a structured questionnaire (Appendix). The questionnaire incorporated a mini-mental state examination to allow recognition of patients who were cognitively impaired at the time of interview[2]. All questions were put to patients by one interviewer (W.V.). Patients did not have sight of the questionnaire forms. Interviews were conducted in hospital during the postoperative period by the same interviewer. Whenever possible, interviews were conducted between 1 and 4 days after operation, at the earliest time at which it was considered that the patient was comfortable enough for such an interview to take place. The interview lasted about 20 min and was conducted with the individual's consent in all cases. Permission was obtained from all consultant surgeons to study patients admitted under their care. Surgeons accepted that they would not be informed of the dates of commencement and completion in order to reduce any potential influence of the study on standard practice.

Patients

Patients over the age of 16 years admitted with acute abdominal pain and undergoing urgent surgery were studied. For the purposes of this study urgent surgery was defined as a procedure performed for a suspected acute abdominal condition where operation could not be deferred and was generally (but not exclusively) performed within 48 h of admission. A consecutive series of 51 patients (33 men) was interviewed. Patients with vascular and urological urgencies were admitted under separate services and are not included. No patient declined to be interviewed. Of these 51 patients, 49 obtained scores of 26 or above in response to the mini-mental state examination. The two who demonstrated evidence of cognitive impairment in response to the mini-mental state examination were an 80-year-old man and an 86-year-old man, both of whom were interviewed 2 days after urgent hernia repair. Both scored 20 from a maximum of 30 in the mini-mental state examination and, as a score of under 25 indicates cognitive impairment[2], they were excluded from further study.

Thus the study population consisted of 49 patients, of whom 31 were male. The median age was 39 (range 16–90) years. The operative procedures undergone by these patients were appendicectomy (29), laparotomy (11), urgent hernia repair

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(five), laparoscopy (one), wound exploration (one), drainage of liver abscess (one) and open cholecystectomy (one). Forty-six patients underwent surgery within 48 h of admission to hospital.

Interviews were conducted a median of 2 (range 1–19) days after operation. No patient was interviewed on more than one occasion. Before surgery all patients signed standard hospital consent forms which were countersigned by the preregistration house officer. There was no other documentation of the consent interview in the notes. As the time of obtaining consent before operation was not recorded in the notes, this study was unable to ascertain whether patients gave consent before or after administration of analgesia. However, no patient in the study underwent surgery without a period of stabilization and assessment on the ward and 48 received preoperative opiate analgesia.

Patients were not asked whether they knew the grade of the doctor obtaining consent as it was established during the questionnaire validation process that the majority were unaware of the grade of the doctor before operation. This general surgical unit employs a partial shift system for preregistration house officers and specialist registrars, and doctors responsible for preoperative care would not necessarily be responsible for postoperative care.

Statistical analysis

Comparison of medians was by the Wilcoxon rank sum test. Ninety-five per cent confidence intervals were calculated using the BMJ software package 'confidence interval analysis'.

Results

Patients' perceptions of factors interfering with the ability to give informed consent

These are listed in *Table 1*. Thirty-one of the 49 patients perceived that preoperative pain had not interfered with their ability to give informed consent. Similarly, 40 of 48 given preoperative analgesia reported this had not affected their ability to give consent. Of the six who reported that analgesia had interfered with their ability to give informed consent, four were in the group of 16 who stated that pain had affected their ability to give consent. Thus a total of 18 perceived that they had been unable to give informed consent either because of pain from the acute abdominal condition or as a result of impaired ability to reason because of analgesia (or both). Although there was no significant difference in the median age of patients affected by pain or the effects of analgesia compared with unaffected patients (41 *versus* 46 years; 95 per cent confidence interval −18 to 8), there were relatively few elderly patients in this study. There was no significant difference in delay to operation or in time between operation and interview between patients reporting an effect of pain and/or analgesia and those perceiving that these factors did not impair their ability to give consent. The types of operation undergone by patients who perceived that they were affected by pain and/or analgesia were: appendicectomy (13), laparotomy (four) and open cholecystectomy (one).

Table 1 Patient perceptions of factors affecting the ability to give informed consent

	Preoperative pain (*n* = 49)	Preoperative analgesia (*n* = 48)	Other (*n* = 49)
Yes	16 (33)	6 (13)	8 (16)
No	31 (63)	40 (83)	41 (84)
Don't know	2 (4)	2 (4)	0 (0)

Values in parentheses are percentages. Four patients reported that a combination of pain and the effects of preoperative analgesia affected their ability to ask questions

The eight patients who replied that 'other' factors affected the consent interview all reported that they had perceived that the medical staff were too busy to provide a detailed explanation or to answer questions. However, these patients perceived that their ability to give informed consent was unaffected by pain or analgesia.

Eighteen of 49 patients stated that they would have asked more or different questions if they had not been in pain. Fourteen of this group were patients who thought that pain had impaired their ability to give informed consent.

Patient comprehension of why an operation was being planned

Forty-two patients stated that they had understood why an operation was being performed while seven replied that they had not. In these seven patients the factors underlying this lack of comprehension were examined further. Three reported that their ability to comprehend was affected by pain. Five of the seven reported lack of explanation by the medical staff as a reason for not understanding why an operation was to be performed. Four of these five attributed the lack of explanation to the fact that the urgency of the situation meant that there was insufficient time for the medical staff to offer any explanation. The median age of the group of seven was 49 (range 20–90) years and the group included three patients over the age of 70 years with four undergoing appendicectomy and three laparotomy. All appendicectomies in this subgroup were carried out within 48 h of admission as were two of the laparotomies.

Discussion of potential side-effects and complications

Twenty-eight patients replied that they had experienced no discussion of any potential side-effects or complications of surgery. The reasons for this lack of discussion were examined in greater detail and three patients reported an inability to comprehend any discussion of side-effects as a result of pain. A further three perceived the medical staff to be unwilling to engage in discussion because of the level of pain being experienced by the patient at the time of the consent interview. The remaining 22 patients stated that no offer had been made by the medical staff to discuss potential side-effects or complications. This group included all seven patients who reported that they had not understood why an operation was to be performed.

Discussion

This study has examined patients' perceptions of the quality of informed consent in the setting of surgery for an acute abdominal condition.

When interpreting the findings of this study it should be borne in mind that the replies represent a qualitative assessment of the informed consent interview. Factors that could induce bias towards better comprehension include the predominance of young patients undergoing appendicectomy and negative factors include the timing of the interview such that answers were recorded after anaesthesia when recall of events before surgery may be affected. Postoperative interview was chosen as a reflection of what the patient 'takes home' and because recall of what was said before surgery in terms of expected outcome may form the basis of subsequent dissatisfaction if unexpected or unexplained outcomes occur.

The study design excluded patients who were cognitively impaired at the time of interview but would not have detected patients who were cognitively impaired at the time of giving consent. Nevertheless the clinicians regarded these patients as able to give signed consent.

These findings demonstrate that preoperative pain did not affect the perceived ability to give informed consent in 31 of 49 patients. Similarly, 40 patients reported that preoperative analgesia did not affect their perceived ability to give informed consent.

Although 42 patients reported that they understood why an operation was to be performed, it is a cause for concern that seven had not understood why they underwent surgery. As this group included three patients over the age of 70 years, cognitive impairment at the time of consent is one possible explanation. However, none of these patients was cognitively impaired within the limitations of the mini-mental state examination at the time of interview.

Similarly, 28 patients reported that they had received no discussion of any potential side-effects or complications of surgery. It may be argued that in patients undergoing laparotomy for an acute intra-abdominal condition it is not possible to give information regarding outcome until the diagnosis has been established. However, most patients in this study underwent urgent appendicectomy and may have benefited from discussion of common complications such as wound infection, likely inpatient stay and the potential for impairment in ability to drive. The majority of patients in this study clearly stated that the reason why they had not understood the potential side-effects and complications of surgery was because there was no discussion of these factors.

In summary, this study constitutes the first structured documentation of patients' perceptions of the informed consent interview in the setting of surgery for acute abdominal pain. As such it provides insight into the consent process in current British general surgical practice. The results demonstrate that most patients perceive that they retained the ability to give informed consent despite the effects of pain and preoperative analgesia. The majority understand the indications for surgery but there is a need for better discussion of potential side-effects and complications of surgery.

Acknowledgements

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Appendix

Perceptions of informed consent in patients with acute abdominal pain

Case note number:
Patient name:
Date of birth:
Date of admission:
Date of operation:
Date of interview:
Questions

If you were in pain before your operation, did this prevent you asking questions about your operation or getting all the information that you wanted?
Did pain affect your ability to think clearly?
Did the effects of painkilling tablets or injections prevent you from asking questions about the surgery?
Did anything else (other than pain or the effects of tablets/injections) prevent you from asking questions about the surgery?
If you had not been in pain would you have asked more or different questions?
Did you understand why an operation was being planned?
If you did not understand why an operation was being planned, why was this?
Were the possible side-effects and complications of surgery discussed with you?
If the possible side-effects and complications were not discussed, why do you think this was?

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Perigastric lymph node status as a prognostic indicator in patients with gastric cancer

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Background The extent of lymph node dissection and histological examination of dissected lymph nodes varies among countries, which leads to the erroneous nodal stage and different surgical results in gastric cancer (stage migration, 'Will Rogers effect'). The aim of this study was to clarify the prognostic significance of the number of positive perigastric lymph nodes, which could be evaluated simply after D_1 gastrectomy.

Methods A consecutive series of 106 patients with histologically node-positive gastric cancer treated by radical gastrectomy and lymph node dissection (D_2 or D_3) was studied. The number of metastatic perigastric nodes (level I, nos 1–6) was examined, and its influence on the survival of patients was analysed.

Results The overall 5-year survival rate was 50·9 per cent; the 5-year survival rate was significantly decreased when positive perigastric nodes exceeded six (62 per cent for one to six nodes *versus* 23 per cent for seven or more nodes, $P < 0.001$). Tumours having one to six positive perigastric nodes compared with those having seven or more positive perigastric nodes were more likely to have a size less than 4 cm (29 per cent *versus* one of 30, $P < 0.001$), grossly localized type (45 per cent *versus* seven of 30, $P = 0.042$), absence of serosal invasion (32 per cent *versus* none of 30, $P = 0.002$) and metastasis limited to the perigastric lymph nodes (70 per cent *versus* seven of 30, $P < 0.001$).

Conclusion The results indicate that the number of positive perigastric nodes correlates with tumour progression and patient survival. This parameter is a simple and useful prognostic indicator for node-positive gastric cancer, and is available not only for D_2 and D_3 gastrectomy but also for D_1 gastrectomy.

The status of lymph node metastasis is significantly associated with the outcome of patients with gastric cancer[1,2]. However, the extent of lymph node dissection and histological examination of the dissected lymph nodes varies among countries[3–5], which leads to erroneous nodal staging and different surgical results (stage migration phenomenon[6], 'Will Rogers effect'[7]). Although sufficient long-term survival data are not yet available, preliminary results from a randomized controlled trial have indicated that D_2 gastrectomy is followed by higher morbidity and mortality rate than D_1 gastrectomy[8,9], and D_1 gastrectomy may be justified as a standard treatment for gastric cancer.

Considering these issues, a simple and easy evaluation system of lymph node metastasis is needed. Recently, the authors clarified that the level of lymph node metastasis was simply classified as perigastric nodes (level I, nos 1–6), intermediate nodes (level II, nos 7–9) and distant nodes (level III, nos 10–16), irrespective of the location of the tumour[10], and that the total number of metastatic lymph nodes was the most important prognostic parameter in node-positive gastric cancer[11].

In this study, the long-term results of 106 curatively treated patients with node-positive gastric cancer were analysed, and the prognostic significance of the number of positive perigastric nodes harvested by D_1 gastrectomy was evaluated. Characteristics of the tumour with regard to the number of positive perigastric nodes were also examined.

Patients and methods

Between 1982 and 1991, a total of 418 patients with primary gastric adenocarcinoma were treated in this department. These patients included 21 who had no operation, 38 who had gastrectomy, 56 who had palliative gastrectomy, and 303 who had curative gastrectomy and lymph node dissection (D_2 or D_3). Since 197 patients had node-negative gastric cancer, 106 patients with node-positive gastric cancer were studied. No patient had liver metastasis; peritoneal dissemination; invasion to the oesophagus, duodenum, pancreas, and mesocolon; or cancer of other organs.

The age and sex of the patient, the site, size, gross type and histological type of tumours, depth of wall invasion, and number and level of positive nodes were obtained from the operation records and histopathology reports. Although these clinicopathological findings were analysed according to the Japanese classification for gastric cancer outlined by the Japanese Research Society for Gastric Cancer[12], the level of lymph node metastasis was simply categorized as perigastric nodes, intermediate nodes and distant nodes, irrespective of the tumour location[10].

Follow-up was continued until death, or for more than 5 years for surviving patients. Only patients who clearly died from recurrent gastric cancer were included in the tumour-related deaths and those who died from other diseases or unknown causes were censored.

The cumulative survival rate was calculated by the Kaplan–Meier method, and the survival curves were compared by the Mantel–Cox method. Statistically significant differences were analysed by the χ^2 test, and independent prognostic factors were tested by Cox regression analysis.

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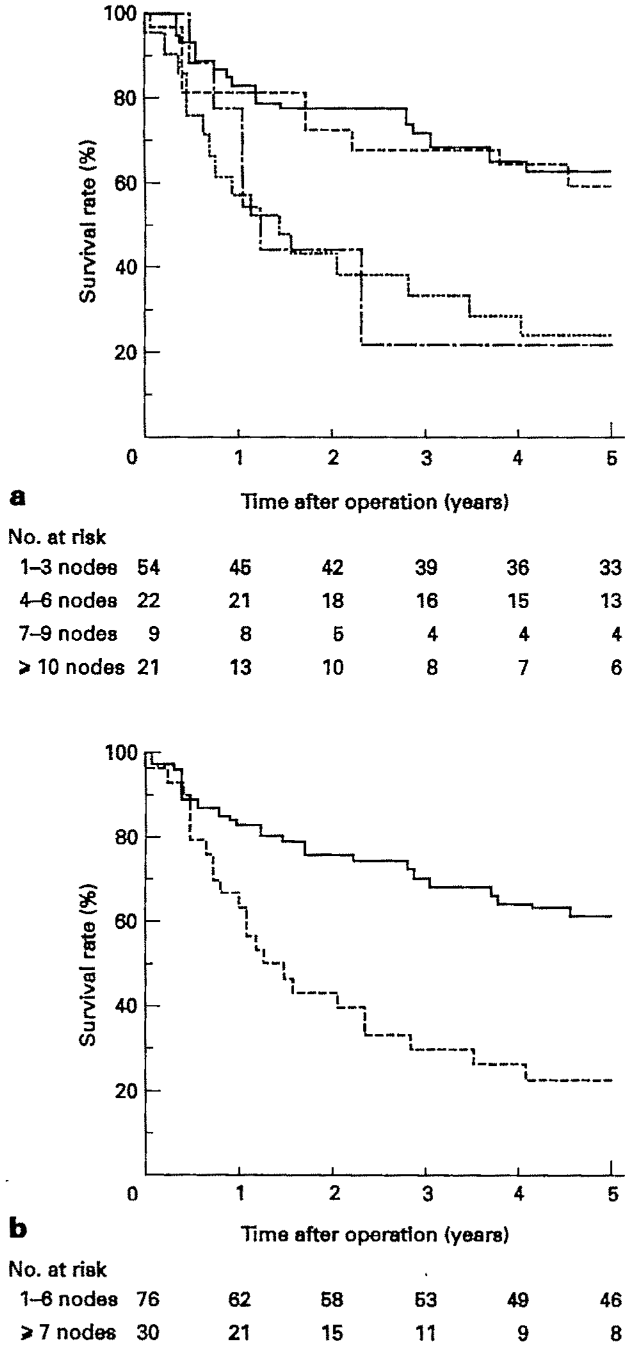
Results

Survival of patients (Table 1, Fig. 1)

Follow-up demonstrated that 47 patients were alive without recurrence, 54 died from recurrent gastric cancer, four died from other diseases (pneumonia ($n = 2$), cardiac failure, liver cirrhosis) and one died from an unknown cause. These five patients died more than 5 years after operation. The overall 5-year survival rate was 50·9 per cent, and the 5-year survival rate decreased significantly when the number of positive perigastric nodes exceeded



No. at risk

1–3 nodes	54	45	42	39	36	33
4–6 nodes	22	21	18	16	15	13
7–9 nodes	9	8	5	4	4	4
> 10 nodes	21	13	10	8	7	6

No. at risk

1–6 nodes	76	62	58	53	49	46
> 7 nodes	30	21	15	11	9	8

Fig. 1 Survival curves according to number of positive perigastric nodes. a ———, one to three nodes; — — —, four to six nodes; —·—·, seven to nine nodes; ·····, ten or more nodes ($P = 0·009$, Kaplan–Meier and Mantel–Cox methods). b ———, one to six nodes; — — —, seven or more nodes. The 5-year survival rate decreased significantly when the number of positive perigastric nodes exceeded six ($P < 0·001$, Kaplan–Meier and Mantel–Cox methods)

Table 1 Number of positive perigastric nodes and survival of patients

No. of positive perigastric nodes	No. of patients	5-year survival rate (%)	*P*
1–3 nodes	54	62	
4–6 nodes	22	59	0·873
7–9 nodes	9	22	0·009
≥ 10 nodes	21	24	0·719
1–4 nodes	59	62	
5–8 nodes	22	50	0·258
≥ 9 nodes	25	24	0·069
1–5 nodes	70	59	
6–10 nodes	15	47	0·159
≥ 11 nodes	21	24	0·156
1–6 nodes	76	62	
≥ 7 nodes	30	23	< 0·001

Survival rate calculated by Kaplan–Meier method and tested by Mantel–Cox method

Table 2 Comparison between one to six and seven or more positive perigastric nodes

	Positive perigastric nodes		
Variable	1–6 nodes ($n = 76$)	≥ 7 ($n = 30$)	*P*
Age (years)			
< 60	36 (47)	12 (40)	
≥ 60	40 (53)	18 (60)	n.s.
Sex			
Male	50 (66)	24 (80)	
Female	26 (34)	6 (20)	n.s.
Site			
Antrum	35 (46)	17 (57)	
Body	33 (43)	11 (37)	
Cardia	8 (11)	2 (7)	n.s.
Size (cm)			
0–3·9	22 (29)	1 (3)	
4–9·9	50 (66)	18 (60)	
≥ 10	4 (5)	11 (37)	< 0·001
Gross type			
Localized	34 (45)	7 (23)	
Infiltrative	42 (55)	23 (77)	0·042
Histological type			
Well differentiated	24 (32)	5 (17)	
Poorly differentiated	52 (68)	25 (83)	n.s.
Depth of invasion			
Mucosa, submucosa	15 (20)	0 (0)	
Muscularis propria	9 (12)	0 (0)	
Subserosa, serosa	52 (68)	30 (100)	0·002
Lymph node metastasis			
Level I	53 (70)	7 (23)	
Level II	17 (22)	10 (33)	
Level III	6 (8)	13 (43)	< 0·001

Values in parentheses are percentages. n.s., Not significant six ($P=0.009$). The 5-year survival rate was significantly different between patients with one to six positive perigastric nodes and those with seven or more positive perigastric nodes (62 per cent *versus* 23 per cent, $P<0.001$). Multivariate analysis showed independent prognostic factors were the depth of wall invasion ($P=0.001$) and level of lymph node metastasis ($P=0.001$) but not the number of positive perigastric nodes.

Characteristics of tumours (Table 2)

Tumours with one to six positive perigastric nodes compared with those with seven or more positive perigastric nodes were significantly characterized by size less than 4 cm (29 per cent *versus* one of 30, $P<0.001$), grossly localized type (45 per cent *versus* seven of 30, $P=0.042$), invasion not beyond the muscularis propria (32 per cent *versus* none of 30, $P=0.002$), and metastasis limited to the perigastric nodes (70 per cent *versus* seven of 30, $P<0.001$).

Discussion

Many authors report that both the number and level of lymph node metastases are useful prognostic factors in gastric cancer[1,2,10,11,13]. However, these factors are influenced by the extent of lymph node dissection and are dependent on meticulous histopathological examination of the dissected lymph nodes[3–5]. The numbering (nos 1–16) and grouping (groups 1–4) of lymph nodes according to tumour location[12] is too complicated to be used routinely in community hospitals. To evaluate the surgical results of gastric cancer in various countries and hospitals, a simple and easy system of lymph node staging is needed.

Recently, the authors proposed a simple classification of lymph node level (levels I, II and III, irrespective of the location of the tumour) and showed that the classification is useful in estimating the prognosis of patients with gastric cancer[10]. Furthermore, it was clarified that the total number of positive lymph nodes is the most important prognostic indicator, and that the level of lymph node metastasis is dependent on the number[11]. It was also demonstrated that Dukes classification for colorectal cancer can be applied successfully to gastric cancer as a useful staging system, and a modified Dukes classification (Dukes A, B, Ca, and Cb, according to the level or number of positive lymph nodes) provides further important prognostic information[14]. Therefore, an attempt has been made to evaluate the relationship between the number of positive perigastric nodes and patient survival or tumour progression, and the usefulness of number of positive perigastric nodes as a prognostic indicator in node-positive gastric cancer.

In the present study, the number of metastatic perigastric nodes was a significant prognostic factor after curative resection of node-positive gastric cancer. This parameter is available not only in patients who have had D_2 or D_3 gastrectomy but also in those who have undergone D_1 gastrectomy. Since this lymph node staging minimizes the effect of stage migration, surgical results of gastric cancer in each hospital can be compared among D_1, D_2 and D_3 gastrectomies[15,16], or among Japanese and Western countries[17,18].

The number of perigastric lymph node metastases was determined by the tumour size, depth of wall invasion and the level of positive nodes, which are generally accepted as important parameters associated with tumour progression and patient survival in gastric cancer[19,20–22]. These findings support the observation that tumours with one to six positive perigastric nodes had a good prognosis, whereas tumours with seven or more positive perigastric nodes were associated with a poor prognosis.

In this study, the number of perigastric lymph node metastases was closely linked to the depth of wall invasion and the level of lymph node metastasis. These two parameters are the most powerful prognostic indicators in gastric cancer[1,2,11]. The authors believe this is why multivariate analysis failed to show the independent prognostic value of perigastric lymph node status. Since the results of multivariate analysis are influenced by the sample size and complex interactions among the variables, prognostic significance of the number of perigastric lymph node metastases must be investigated further in a larger series of node-positive gastric cancers.

In conclusion, the number of positive perigastric nodes is a simple and useful prognostic indicator in node-positive gastric cancer. This parameter may be applied to patients who have had a D_1 gastrectomy, and will contribute to evaluating and comparing surgical results among various surgeons and countries.

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Gastric carcinoid expresses the gastrin autocrine pathway

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Background In gastric adenocarcinoma the gastrin autocrine–paracrine pathway is activated. As enterochromaffin-like (ECL) cells originate from the same stem as epithelial cells, the aim of this study was to determine if the gastrin autocrine pathway is present in gastric carcinoid.

Methods Samples from ten patients with gastric carcinoid were assessed by immunocytochemistry using primary antibodies directed against gastrin precursors and the gastrin/cholecystokinin B receptor and detected using the avidin–biotin immunoperoxidase system.

Results A high level of expression of precursor and mature gastrin peptides, together with the gastrin receptor, was seen in all carcinoids screened.

Conclusion In common with the glandular epithelium of the stomach the gastrin gene is activated during the neoplastic process in ECL cells. This finding may explain why some carcinoids do not regress after surgical procedures that lower serum gastrin. Antigastrin agents may be a useful treatment for carcinoid either in their own right or as an adjunct to surgery.

Gastric carcinoid results from overproliferation of the histamine-containing endocrine cells of the fundus, the enterochromaffin-like (ECL) cells. The first two cases of gastric carcinoid were reported by Askanazy in 1923[1]. Until recently, gastric carcinoids were considered to be rare tumours accounting for no more than 0·3 per cent of all gastric tumours and 3 per cent of gastrointestinal carcinoids[2–5]. The prevalence of gastric endocrine tumours has increased with the advent of endoscopy for the investigation of upper abdominal symptoms and the introduction of gastroscopic screening among patients with pernicious anaemia and chronic atrophic gastritis[6–8]. It is now thought that they may comprise between 10 and 30 per cent of gastrointestinal carcinoids[5,9].

In the normal physiological state the ECL cell plays a central role in the control of acid secretion. Gastric acid secretion is controlled by a negative feedback mechanism (*Fig. 1*)[10]. Food in the stomach stimulates the secretion of gastrin from G cells by a minimum of three mechanisms; direct chemical stimulation by peptides and amino acids, antral distension and by an increase in the intragastric pH[11,12]. Secreted gastrin acts in an endocrine manner to stimulate ECL cells to secrete histamine by interaction with gastrin/cholecystokinin B (CCKB) receptors. In turn, histamine stimulates fundic parietal cells to secrete acid. As the antral pH falls, gastrin release is reduced, stopping at a pH of 2·5, thus completing the negative feedback cycle[12]. In addition to stimulating acid secretion, gastrin is trophic for oxyntic gastric mucosa[13]. Loss of gastrin leads to atrophy, while hypergastrinaemia leads to hypertrophy of all the cellular elements in oxyntic mucosa.

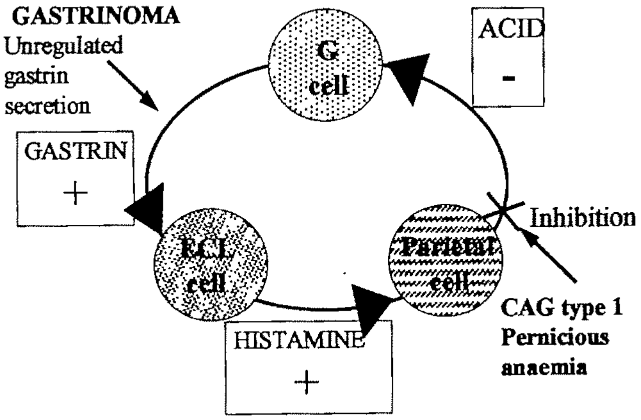

Fig. 1 Control of gastric acid secretion; the negative feedback mechanism. Vagal and paracrine pathways are not shown. ECL, enterochromaffin-like; CAG, chronic atrophic gastritis

The majority of gastric carcinoids occur in patients with conditions associated with hypergastrinaemia; pernicious anaemia associated with chronic atrophic gastritis and Zollinger–Ellison syndrome (ZES) in multiple endocrine neoplasia type 1 (MEN1). Simple hypergastrinaemia leads to ECL cell hyperplasia, but in most cases an additional factor is necessary for transformation of ECL cells into the neoplastic state. In pernicious anaemia this transformation is thought to be due to the presence of autoantibodies; several autoantibodies have been identified including the classical antiparietal and anti-intrinsic factor antibodies[14], and specific autoantibodies against the gastrin/CCKB receptor and subunits of the hydrogen–potassium adenosine $5'$-triphosphatase proton pump[15]. One particular antibody has not been implicated. Furthermore in ZES the underlying genetic abnormality in MEN1 is required for ECL cell transformation.

The hormone gastrin is now a recognized growth factor for several cancer types including gastric adenocarcinoma. This proliferative action of gastrin has been demonstrated *in vitro* in several gastric cancer cell lines[16–18] in primary human gastric tumour tissue[19,20] and has been confirmed in *in vivo* xenograft models[21–23].

In gastric adenocarcinoma, the gastrin gene is activated in the tumour cells[22,24] with unregulated production and secretion of both precursor gastrin species and mature amidated gastrin[25–27] (*Fig. 2*). Mature and precursor gastrin forms have a proliferative action[28–32], mediated via

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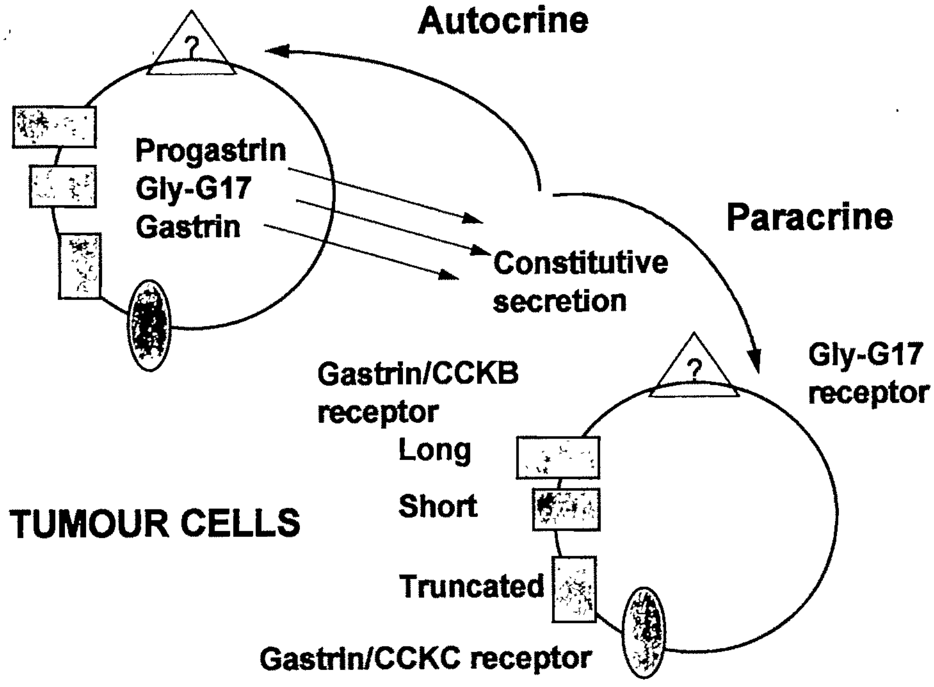

Fig. 2 The gastrin autocrine/paracrine pathways operating in tumour cells. Gly-G17, glycine extended gastrin-17; CCKB, cholecystokinin B; CCKC, cholecystokinin C

autocrine or paracrine pathways[33,34]. The action of these peptides is mediated by a number of receptor subtypes, including receptors that have yet to be fully characterized[35–37].

ECL cells express gastrin/CCKB receptors, but the only known mediator stored and secreted from ECL cells is histamine[38]. Thompson *et al.*[39] have shown that all cells in the gastric mucosa are the product of a single undifferentiated stem cell. The aim of this study was to determine if the gastrin autocrine pathway is expressed in ECL cells following transformation to the malignant phenotype.

Patients and methods

Samples were obtained from ten patients with gastric carcinoid (six women, four men; median age 53 (range 24–73) years) between 1986 and 1994. Serial sections cut from each paraffin block were stained with haematoxylin and eosin for morphological examination and Grimelius' silver-impregnation stain for agyrophil endocrine cell detection by a histopathologist, confirming the diagnosis of carcinoid. The carcinoids were grouped according to Rindi *et al.*[5]. Eight carcinoids were secondary to pernicious anaemia and there was associated atrophic gastritis. The agyrophil cells not associated with the tumour showed linear and micronodular hyperplasia in seven of eight cases. Serum gastrin levels were not measured in these patients. In two patients the carcinoids appeared to be sporadic; circulating gastrin levels were normal and there was no evidence of pernicious anaemia or ZES. The surrounding agyrophil cells showed no evidence of hyperplasia. One patient with sporadic carcinoid had associated liver metastases.

Immunohistochemistry

Biopsies from normal gastric antrum and fundus obtained from patients undergoing endoscopy for symptoms of dyspepsia were found to be normal and were used as positive controls for gastrin expression (in G cells) and gastrin/CCKB receptor expression (in ECL and parietal cells). No *Helicobacter pylori* were seen on histological examination of the control samples.

Paraffin-embedded sections (5 μm) were adhered to glass-coated slides, dewaxed, deparaffinized and rehydrated in alcohol. The sections were then incubated in 10 per cent hydrogen peroxide in methanol for 15 min at room temperature to quench endogenous peroxidase, followed by two further alcohol washes and a 1-min water soak. The sections were then blocked in swine serum (DakoPatts, Cambridge, UK) for 20 min at room temperature, the excess serum was removed and the sections were incubated for 60 min with either 1/100 diluted antiamidated gastrin-17, 1/80 diluted antiglycine-extended gastrin-17, 1/40 diluted antiprogastrin antisera or 1/40 antigastrin/CCKB receptor, gastrin receptor peptide 1 (GRP1), antiserum (directed against the amino-terminal domain of the human gastrin/CCKB receptor) with and without preabsorption with the GRP1 peptide (Aphton Corporation, Woodland, California). The antisera against the different gastrin species have been characterized previously by immunoprecipitation and high-pressure liquid chromatography[40]. The antigastrin receptor antiserum has been characterized by Western blotting[41]. Excess primary antibody was removed by two 5-min soaks in phosphate-buffered saline (PBS) (pH 7·2). Biotinylated rabbit antimouse immunoglobulin and horseradish peroxidase-conjugated avidin antibody (Dako, DakoPatts) were consecutively applied to the sections for 30 min at room temperature. The sections were washed in PBS twice between each step. Peroxidase activity was identified by applying 3,3′-diaminobenzidine tetrachloride for 10 min at room temperature. The sections were then rinsed in water, soaked for 10 min in copper sulphate, then counterstained with haematoxylin. Finally the sections were dehydrated, cleared and mounted with coverslips.

The sections were assessed blind by two independent observers. The site of staining was recorded. The degree of staining was assessed on an ordinal scale from 0 to 6.

Results

As expected the gastric antrum control showed expression of gastrin in G cells; this was evident as discrete, intense cytoplasmic staining, but there was no expression of the gastrin/CCKB receptor. In the normal fundus, there was no expression of gastrin, but the gastrin/CCKB receptor was observed on ECL and parietal cells (recently also demonstrated by Reubi *et al.*[42]), with staining located within the cytoplasm and nucleus. Similar staining was seen in the gastric fundic epithelial cells and stem cells of the gastric pit (*Fig. 3*). Staining intensity for the gastrin/CCKB receptor is greatest at the nucleus. This is a result of rapid internalization and translocation following ligand binding to the receptor; this movement has been confirmed by dynamic electron microscopy[43].

All of the carcinoids expressed the gastrin/CCKB receptor with definite nuclear immunoreactivity and weaker cytoplasmic staining as described above. An example of a typical staining pattern is shown in *Fig. 4*. There was very strong expression of progastrin (*Fig. 5*), glycine-extended gastrin-17 and mature amidated gastrin-17 in the cytoplasm of the tumour cells. The immunohistochemical results are summarized in *Table 1*. All species investigated were seen in all of the carcinoid samples examined. The intensity of immunoreactivity was also high (4–6 on an arbitrary scale) for each molecule in all samples.

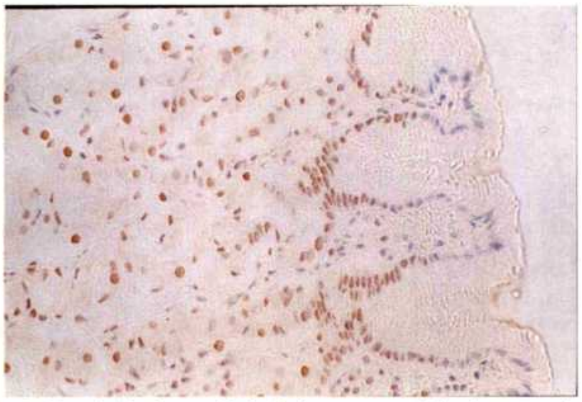

Fig. 3 Gastrin/cholecystokinin B immunoreactivity in normal gastric fundus demonstrating definite nuclear staining and weaker cytoplasmic staining in enterochromaffin-like, parietal and stem cells of the gastric pit. (Original magnification × 250)

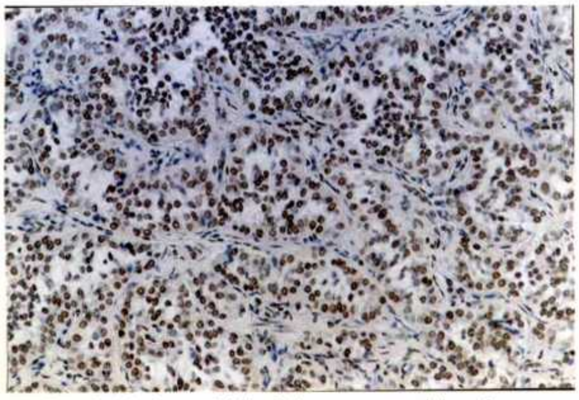

Fig. 4 Gastrin/cholecystokinin B immunoreactivity of a representative gastric carcinoid tumour. (Original magnification × 100)

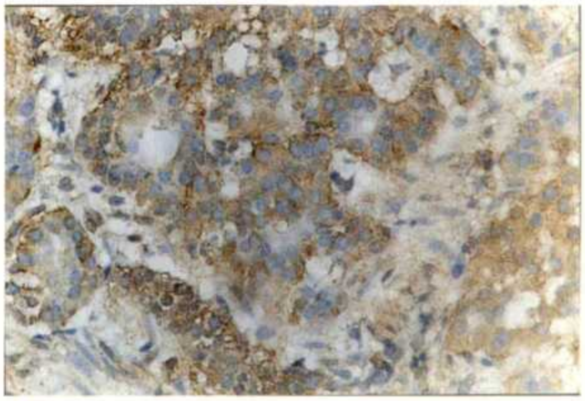

Fig. 5 Progastrin immunoreactivity of a representative gastric carcinoid tumour. (Original magnification × 400)

Table 1 Expression of gastrin peptides and the gastrin/cholecystokinin B receptor by gastric carcinoids

Immunoreactive molecule	Percentage of samples expressing molecule	Intensity of immunoreactivity*
Progastrin	100	4
Gly-gastrin-17	100	5
Amidated gastrin-17	100	4
Gastrin/CCKB receptor	100	6

*0–6 on an ordinal scale. CCKB, cholecystokinin B

Discussion

The findings show that, following malignant transformation of the ECL cell, the gastrin gene is activated, providing all the components necessary for the potential operation of the gastrin autocrine pathway.

At present, treatment for gastric carcinoid entails regular endoscopic surveillance for small lesions[44–46], endoscopic fulgaration[8,47,48], surgical excision or gastric antrectomy to lower gastrin levels[5,49]. Antrectomy generally results in normalization of the raised gastrin levels which initially cause the ECL cell to hyperproliferate[50]. However, only approximately half of the patients with carcinoid respond to normalization of systemic gastrin levels and the responders still require regular endoscopic follow-up[51]. Antrectomy should be limited to patients with low-grade carcinoids, as in general no effect is seen on large, locally invasive or metastatic carcinoids. The failure of a procedure designed to lower circulating gastrin may in part be explained by the autocrine production of gastrin, which in turn is dependent upon the degree of differentiation. Carcinoids expressing the gastrin/CCKB receptor may respond to both autocrine and endocrine pathways. If the tumour is well differentiated (reflective of low-grade carcinoids) then the autocrine pathway may not be developed enough to support growth. This concept is supported by a recent paper by Tang *et al.*[52], who demonstrated in the *Mastomys* genus model of gastric carcinoid that there is progression to independence of endocrine hypergastrinaemia.

A possible alternative to endoscopy or surgery may be to neutralize gastrin. This can be carried out effectively using an antigastrin immunogen that produces *in situ* antibodies against the active forms of gastrin. This technique has the advantage that it neutralizes both the circulating and tumour-associated autocrine gastrin. Therefore this approach would target both primary and metastatic carcinoid deposits.

In conclusion, identification of the presence of an autocrine pathway in gastric carcinoids may clarify the failure of current treatment in certain cases and highlights the need for alternative treatments for such patients.

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Oesophageal dysmotility is not associated with poor outcome after laparoscopic Nissen fundoplication

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Background Nissen fundoplication has become the standard operation in the surgical management of gastro-oesophageal reflux disease. Postoperative dysphagia is thought to occur more commonly in patients with oesophageal dysmotility and it has been recommended that fundoplication be modified or avoided in these patients. The aim of this study was to determine the outcome of patients with normal motility and dysmotility undergoing laparoscopic Nissen fundoplication.

Methods This was a single-centre prospective cohort study with 1-year follow-up, using dysphagia as the main outcome variable. Of 81 patients who underwent laparoscopic surgery, 48 had normal motility and 33 had oesophageal dysmotility (defined as percentage peristalsis, using ten wet swallows, of 50 per cent or less and/or a mean distal pressure of less than 40 mmHg).

Results Dysphagia was present before operation in 14 of 48 patients with normal motility and 15 of 33 in the dysmotility group ($P = 0{\cdot}2$). At 3-month follow-up, new or worse dysphagia was present in 13 of 48 patients in the normal group and four of 33 in the dysmotility group ($P = 0{\cdot}17$). At 1 year the incidence of dysphagia was six of 48 in the normal group and five of 33 in the dysmotility group ($P = 0{\cdot}9$).

Conclusion Preoperative manometric assessment of oesophageal motility does not correlate with postoperative outcome, and oesophageal dysmotility should not be regarded as a contraindication to laparoscopic Nissen fundoplication.

Laparoscopic antireflux surgery has become an acceptable treatment for gastro-oesophageal reflux disease (GORD) requiring long-term maintenance treatment with proton pump inhibitors (PPI) to control symptoms and prevent complications. The main side-effect from fundoplication is new or more severe dysphagia, which affects 10–40 per cent of patients in the first few months after operation[1,2], and around 10 per cent of patients in the long term[3,4].

It has been suggested that patients with abnormal peristalsis on manometric assessment are at high risk of postoperative dysphagia[5,6] and that antireflux surgery should be avoided altogether in patients with severe motility disorders on the premise that they are more likely to develop dysphagia[6–8]. Others recommend a partial fundoplication such as a Toupet[9,10] or a Belsey type procedure[11,12], rather than the 360° Nissen fundoplication, as a precaution in patients with dysmotility, although even supporters of this approach admit that there are no data to support these assumptions[9].

This study compared prospectively the outcome of patients with normal and abnormal oesophageal body motility after laparoscopic Nissen fundoplication.

Patients and methods

Patients

Eighty-one consecutive patients were studied prospectively. The mean age was 43 (range 15–69) years and 46 were men. All patients had a history of long-standing GORD (median 3 years) requiring maintenance treatment with a PPI.

Assessment

Patients were assessed independently by a physician gastroenterologist and a clinical scientist using a standard symptom questionnaire and visual analogue scales (0, no symptom; to 10, severe symptom) for heartburn, dysphagia, regurgitation and nocturnal symptoms (wheeze, choking or cough). Endoscopy, barium swallow and 24-h ambulatory pHmetry (at least 2 weeks after cessation of PPIs) were performed before surgery. The 24-h ambulatory pH monitoring was performed using the Synectics Medical ambulatory pH monitoring system (Synectics Medical, Stockholm, Sweden). The pH electrode was positioned 5 cm above the manometrically determined proximal margin of the lower oesophageal sphincter (LOS) and patients were instructed to pursue normal activities. There were no dietary restrictions and patients used a diary to record meal times, recumbent positions and any symptoms. Data were analysed with the Synectics Esophagram program (Esophagram Software Package; Gastrosoft, Chicago, Illinois, USA). A DeMeester score of more than 14·8 and/or a pH of less than 4 for more than 5 per cent of the study period were considered abnormal[13].

Manometry

Manometry was carried out after an overnight fast using a standard triple-lumen water perfusion catheter (Synectics Medical) passed through the nose. The catheter was connected in series to a low-compliance microcapillary infusion system (JB Biomedicals, Ventura, California, USA) constantly perfused with distilled water at 0·5 ml/min by an Arndorfer pneumohydraulic pump (Arndorfer Medical Specialities, Wisconsin, USA). The LOS length and pressure were measured using the standard station pull-through technique. The catheter was then repositioned with the distal port 5 cm above the proximal border of the LOS and oesophageal body peristalsis was assessed using ten wet swallows with 5-ml aliquots of water at 30 s intervals. Peristaltic activity was defined as a sequential series of pressure waves in response to a wet swallow producing a contraction

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Table 1 Outcome of fundoplication

	Normal motility			Dysmotility		
	Preop.	Postop.	*P*†	Preop.	Postop.	*P*†
Heartburn VAS*	9(2)	0(0·4)	<0·001	8(2)	0(0)	<0·001
Time <pH 4 percentage (%)	15(10)	1(3)	<0·001	13(6)	0(0)	<0·001
DeMeester score	55(36)	4(10)	<0·001	47(22)	2(2)	<0·001
LOS length (cm)	1·6(1·3)	3·5(0·8)	<0·001	1·4(1·4)	4·0(0·7)	<0·001
LOS pressure (mmHg)	3·5(3·0)	13·0(6·4)	<0·001	4·4(5·0)	14·0(5·5)	<0·001

Values are mean (s.d.) or *medians (s.d.). VAS, visual analogue scale; LOS, lower oesophageal sphincter. †Unpaired *t* test. Comparison of normal and dysmotility groups using unpaired *t* test revealed no significant difference in preoperative or postoperative data

amplitude of 10 mmHg or more in the mid and distal ports. Oesophageal dysmotility was defined as peristalsis of 50 per cent or less and/or mean distal oesophageal pressure of less than 40 mmHg.

Surgical technique

The surgical technique was similar to that described by Hinder *et al.*[14] and only the important points in the technique are given here. After insufflation of the peritoneal cavity and dissection of the oesophageal hiatus, the crura were approximated with a single 2/0 Ethibond (Ethicon, Edinburgh, UK) suture. In the majority of patients ($n = 65$) the fundus of the stomach was fully mobilized by routinely dividing the upper short gastric vessels for approximately 10 cm along with any adhesions to the posterior wall of the fundus. Sixteen patients operated on early in the series (11 with normal motility and five with dysmotility) did not have division of the short gastrics routinely as it was felt that the fundus was mobile enough to allow a floppy fundoplication. A 2-cm loose fundoplication was fashioned with two 2/0 Ethibond sutures, with a third suture fixing the right component of the wrap to the oesophagus to prevent rotation. Drains and nasogastric tubes were not used and patients were allowed free access to fluids on the first day after operation, and given a soft diet on day 2.

Although surgeons were not blinded to the preoperative manometric findings, the operation was aimed at creating a short loose wrap in a standard fashion for each patient. To ensure standardization of the technique, all procedures were performed by, or with the assistance of, the senior surgeon (P.C.B.).

Follow-up

Postoperative follow-up was performed at 3 and 12 months using the same questionnaire and visual analogue scores. Dysphagia scores of 0–3 were categorized as mild, 4–6 as moderate, and 7–10 as severe. Follow-up was complete at 3 months and three patients were lost to follow-up at 1 year (one dysmotility, two normal motility group). At the 3-month reassessment patients were invited to undergo repeat manometry and pHmetry.

Statistical analysis

The χ^2 test was used to compare categorical data, and the two-tailed Student's *t* test was used to compare continuous variables.

Results

Surgery

Five patients (four of the first 20 cases) required conversion to an open procedure for adhesions (one), bleeding (two) and poor visualization (two). Data are included in the final analysis based on the intention to treat principle.

Reflux scores and pHmetry

There was significant improvement in the reflux-related symptoms and the pHmetry data after operation, with no significant difference between the normal and dysmotility groups (*Table 1*).

Manometry

Based on the preoperative manometric criteria 48 patients had normal motility and 33 had abnormal motility (dysmotility group). Preoperative and postoperative manometry data were available for 61 patients: 35 of 48 in the normal motility group and in 26 of 33 in the dysmotility group. There was a significant increase in LOS length and pressure in both groups (*Table 1*). There was no significant difference in the preoperative and postoperative oesophageal body manometric findings in the normal motility group. The percentage of propagated peristalsis (*Fig. 1*) and the mean distal oesophageal pressure (*Fig. 2*) in the dysmotility group improved significantly.

Dysphagia scores

Dysphagia was present before operation in 14 of 48 patients in the normal motility group and 15 of 33 in the dysmotility group ($\chi^2 = 1{\cdot}6$, 1 d.f., $P < 0{\cdot}2$). Three months after Nissen fundoplication new or more severe dysphagia was present in 13 of 48 patients with normal motility and four of 33 with dysmotility ($\chi^2 = 1{\cdot}8$, 1 d.f., $P < 0{\cdot}17$).

Seven patients required postoperative dilatation within the first 3 months for moderate or severe dysphagia, five

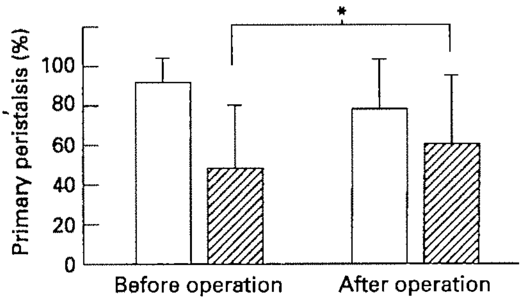

Fig. 1 Mean(s.d.) percentage of primary peristalsis in patients with normal motility (☐) or dysmotility (▨) before and after operation. *$t = 2{\cdot}55$, $P < 0{\cdot}014$ (paired *t* test)

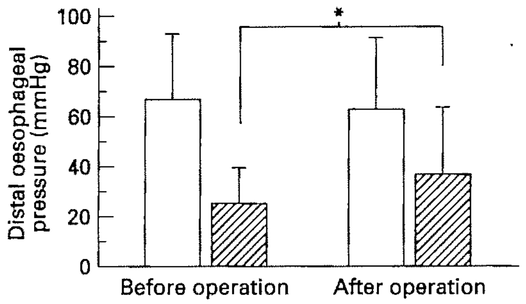

Fig. 2 Mean(s.d.) distal oesophageal pressure in patients with normal motility (□) or dysmotility (▨) before and after operation. $^*t = 2{\cdot}44$, $P < 0{\cdot}022$ (paired t test)

in the normal motility group and two in the dysmotility group. Two patients have undergone further surgery, both of whom had preoperative dysphagia; one patient with abnormal motility had worse dysphagia at 3 months and underwent conversion of the Nissen fundoplication to a 270° fundoplication (Toupet procedure), with improvement but residual intermittent episodes of bolus obstruction; the other patient had normal preoperative motility but severe postoperative dysphagia and elected to undergo conversion to a partial fundoplication.

At 1 year, six of 48 patients in the normal group had dysphagia (three mild, two moderate and one severe awaiting further surgery) with two further patients lost to follow-up. In the dysmotility group five of 33 patients had dysphagia (two mild, two moderate, one moderate after further surgery) and one was lost to follow-up. The prevalence of dysphagia at 1 year in the normal and dysmotility groups was not statistically different ($\chi^2 = 0{\cdot}0002$, 1 d.f., $P < 0{\cdot}9$).

Subgroup analysis was performed to ascertain whether using more strict manometric criteria of dysmotility could identify patients with a worse outcome. Sixteen patients had severe dysmotility defined as 50 per cent or less propagated peristalsis and a mean contraction amplitude of less than 20 mmHg, five of whom had no peristalsis. There were three cases of new or worse dysphagia in this group at the 3-month assessment which was not significantly different compared with the group with normal motility ($n = 48$) ($\chi^2 = 0{\cdot}11$, 1 d.f., $P < 0{\cdot}74$). At 1 year, five patients in this severe dysmotility group had dysphagia compared with 11 in the normal motility group ($\chi^2 = 1{\cdot}79$, 1 d.f., $P < 0{\cdot}18$). All five of the patients with no peristalsis before operation had an improvement in motility following fundoplication, with a median postoperative peristalsis of 50 (range 10–100) per cent at 3 months.

Discussion

There is a high incidence of early postoperative dysphagia after fundoplication[1,2]. Although the majority of cases will improve with time, it is a cause for much anxiety to both the patient and surgeon and may lead to prolonged convalescence, defeating a major objective of laparoscopic surgery. The importance of attention to technical details to produce a short, loose fundoplication is well recognized, although the role of mobilization of the fundus in avoiding postoperative dysphagia remains controversial[14–16]. The authors continue to divide the short gastric vessels to ensure maximum mobility of the fundus during the wrap.

Avoidance of Nissen fundoplication in patients with preoperative dysphagia or manometric abnormalities has been advocated and practised by many surgeons[5–12,17,18]. There are no prospective data to support this conjecture, and the available data tend to refute this assumption. Mughal *et al.*[19] published a prospective analysis of 126 patients undergoing open Nissen fundoplication and found no difference in outcome between patients with various abnormalities: competent cardia, upright reflux or motility disorder (50 per cent or less propagated peristaltic waves; 14 patients). Most recently Baigrie and colleagues[20] prospectively analysed 31 patients undergoing laparoscopic fundoplication and showed new or persistent dysphagia in only two at 1 year with overall satisfaction in 28 patients.

Defining normal and abnormal oesophageal motility remains difficult and the usefulness of these classifications in clinical terms has been questioned recently[21]. For example, patients with complete failure of progresson of peristaltic waves on all ten wet swallows would be regarded by most authors as having severe dysmotility. However, in this study and others[20] a number of patients with no peristalsis have successfully undergone fundoplication, without the development of dysphagia and with improvement in peristalsis after operation. The criteria for defining dysmotility used in the present study were based on data from Kahrilas *et al.*[22] who defined the normal range for failure rates of primary peristalsis (upper limit of 95 per cent confidence interval (c.i.) 51 per cent or more) and the distal oesophageal pressure (lower limit of 95 per cent c.i. 40 mmHg or greater). These criteria of dysmotility have been used by clinicians to modify their operative procedure in the so-called 'tailored approach' to antireflux surgery[9,11,12].

An important finding in this study is the significant improvement in primary peristalsis and distal oesophageal pressures after operation in patients with preoperative dysmotility. There are conflicting reports on the effect of fundoplication on motility with studies ranging from no change[23–25] to significant improvement[26]. Some of these studies have insufficient power to demonstrate a statistical difference and few have analysed the outcome of the dysmotility group separately from that of the normal motility group, which may account for some of the differences between studies. One hypothesis for the improvement in oesophageal motility has been suggested to be improvement in oesophageal sensation secondary to healing of oesophagitis[27,28]. In the present study, however, all patients had been on long-term PPIs and thus overt oesophagitis was not present at the time of manometry. This is supported by findings in patients with GORD and endoscopically proven oesophagitis treated by fundoplication or medical treatment alone, in whom the distal oesophageal pressure was significantly increased after healing of oesophagitis in the surgical group but unaltered in the medical group[23]. The increased pressure imposed by the fundal wrap may cause increased resistance to oesophageal emptying with the oesophagus responding like any other smooth muscle organ by increasing its contractility to overcome this, and thus increasing the force of contraction. The authors propose an alternative hypothesis, namely that reduction of the hernia with lengthening of the lower oesophagus contributes to improving the contractile function of the oesophageal smooth muscle, in a manner reminiscent of the Starling principle in cardiac muscle.

What then is the role of manometry in the assessment of patients for laparoscopic fundoplication? There are three arguments cited for the use of routine oesophageal manometry: as an aid to the diagnosis of GORD; to avoid surgery in patients with alternative diagnoses; and to avoid surgery in patients at 'high risk' of developing postoperative dysphagia. Because there is substantial overlap between normal and abnormal LOS values, manometry can support but not make a diagnosis of GORD[21]. Although fundoplication has been performed mistakenly on patients with achalasia or scleroderma, a careful history will reveal symptoms such as dysphagia allowing selective rather than routine manometry[28].

The results of the present study support the accumulating prospective data[19,20] showing that even severe oesophageal motility is not a predictor of poor outcome, and thus none of these arguments supports the practice of *routine* manometry. Furthermore, oesophageal manometry is expensive[29,30], time consuming[30] and uncomfortable for the patient. Based on the results of this present study it is proposed that oesophageal manometry should be used selectively in the preoperative assessment of patients undergoing antireflux surgery, namely for those patients with a history of dysphagia, with atypical symptoms, and those responding poorly to PPI therapy.

Acknowledgements

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British Journal of Surgery 1998, 85, 1294–1298

Natural history of adhesional small bowel obstruction: counting the cost

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Background The aim of this study was to identify patients admitted with adhesional obstruction to determine if there was an identifiable pattern to the type of initial operation, the type of treatment used for the obstructive episode and the subsequent need for further treatment.

Methods Patients with adhesional obstruction were identified retrospectively in a cross-sectional study using ICD codes relating to admissions in the years 1990 to 1996. The case notes were used to assess their outcome.

Results Fifty-nine case notes from a total of 175 identified initially satisfied the inclusion criteria. These patients had a mean age at presentation of 51 (range 16–88) years and had undergone a total of 122 operations. Thirty-one patients (53 per cent) had a single previous operation with a median time to presentation with obstruction of 5·5 years (range 11 days to 34·7 years); 33 patients (56 per cent) were treated conservatively on their first admission. There was no statistically significant difference in the outcome in patients who received either conservative or surgical treatment. The length of stay in patients treated surgically (median 11 (range 2–47) days) was significantly longer than that for those treated conservatively (median 6 (range 1–39) days) ($P < 0.001$). A flow chart was constructed demonstrating the eventual outcome of the patients in the study, enabling the cost of adhesional obstruction to be calculated.

Conclusion This type of approach could be used to assess the potential effect of different treatment strategies for adhesional obstruction.

The prevention of postoperative intra-abdominal adhesions is a subject which has attracted a great deal of interest over the years. Postoperative adhesions have become a major source of morbidity following laparotomy and are the most common cause of small bowel obstruction in the Western world. Similarly, pelvic adhesions are a frequent problem in patients suffering from subfertility. A recent survey of 750 German hospitals demonstrated that 2·6 per cent of laparotomies were for adhesional bowel obstruction[1] and Ray *et al.*[2] estimated that in 1988 the cost of treatment for lower abdominal–pelvic adhesionolysis in the USA was in excess of $1000 million.

A prospective study by Menzies and Ellis[3] indicated that approximately 1 per cent of patients will suffer obstruction within a year of abdominal surgery and that over a third of people who develop adhesional obstruction will do so within a year of surgery, with the remainder presenting with an initial episode of obstruction at a steady rate up to 10 years after surgery. This suggests an overall rate of adhesion-related morbidity of 3 per cent. An issue yet to be resolved is the risk of recurrence of adhesional obstruction whether it is treated conservatively or by further surgical intervention. Is there evidence to support the old surgical aphorism that 'operations for adhesions cause bigger and better adhesions'? By following a cohort of patients, as in the present study, it has been possible to estimate the likely outcome over a prolonged period of time. This could allow a calculation of the potential effects of different treatment strategies for adhesional obstruction.

Patients and methods

This was a retrospective cross-sectional review of the case notes of patients presenting with obstruction to this hospital. The cases were identified by their ICD (International Classification of Diseases) codes and *Table 1* shows the codes included and excluded. Initially all case notes with the appropriate coding were identified from the year 1996 but this yielded a relatively small number of cases. To increase the number of cases for the study, the same process was applied to all preceding years as far as 1990.

Patients were included in the study if they had been admitted with obstructive symptoms or signs which were deemed to be due to previous surgery and were excluded if the obstruction was caused by any other process. Patients with 'congenital' adhesions

Table 1 Inclusion and exclusion criteria, ICD codes

Included	
ICD 10 K56.6	Other and unspecified intestinal obstruction
ICD 9 560.8	Adhesive and other intestinal obstruction
ICD 9 560.9	Unspecified intestinal obstruction
Excluded	
ICD 10 C18.0–C18.9	Malignant neoplasms of the colon
ICD 10 C20	Malignant neoplasms of the rectum
ICD 10 C17.0–C17.9	Malignant neoplasms of the small intestine
ICD 10 C19	Malignant neoplasms of the recto-sigmoid junction
ICD 9 152.0–152.9	Malignant neoplasms of the small intestine including duodenum
ICD 9 153.0–153.9	Malignant neoplasms of the colon
ICD 9 154.0–154.8	Malignant neoplasms of the rectum and rectosigmoid junction and anus

Paper accepted 4 March 1998

were included only if release of the congenital band went on to form adhesional obstruction.

The following details were recorded: (1) patients' demographics; (2) number and type of operations previous to the first episode of adhesional obstruction; (3) type of treatment (surgical or conservative) for each episode of obstruction and, if the treatment was surgical, details of either the resection or adhesiolysis performed; and (4) length of hospital stay for each episode.

Statistical analysis

Comparison of the types of treatment, lengths of stay and number of readmissions was made using the χ^2 test. Statistical significance was accepted at $P < 0\cdot05$.

Results

One hundred and seventy-five sets of case notes were reviewed of which 59 were felt to satisfy the inclusion criteria for the study. The remaining 116 were rejected. The mean age at first presentation with adhesional obstruction was 51 (range 16–88) years. The diagnosis of adhesional obstruction was made by the clinicians responsible for the patients at the time of admission.

Frequency of previous surgery

The 59 patients underwent a total of 122 operations before the first episode of obstruction. Thirty-one patients (53 per cent) had a single previous operation, 13 (22 per cent) had two operations and three patients had undergone six abdominal procedures before the first admission for adhesional obstruction (*Fig. 1*).

Type of previous surgery

The type of previous surgery was recorded and 11 different categories were identified (*Fig. 2*). The most numerous previous operations were of an upper gastrointestinal nature (consisting mainly of small bowel resections and peptic ulcer surgery) in 38 patients, lower gastrointestinal (consisting of colonic resections) in 26 patients and gynaecological procedures in 17 patients. Five patients had undergone two types of procedure during a previous operation before the first obstructive episode and each of these patients was therefore included in both categories, which increased the total number of procedures performed from 122 to 127 in the 59 patients. In the group of patients who had undergone a single previous procedure ($n = 31$), there were ten colorectal procedures, seven upper gastrointestinal procedures, five appendicectomies and three gynaecological procedures.

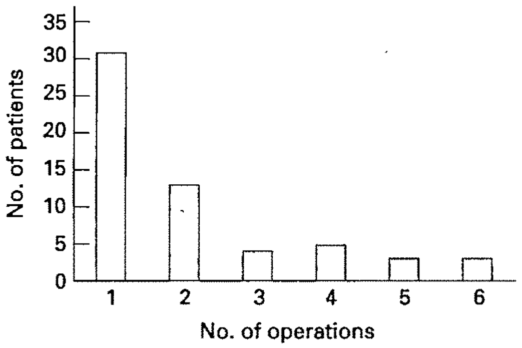


Fig. 1 Number of operations before the first admission for obstruction

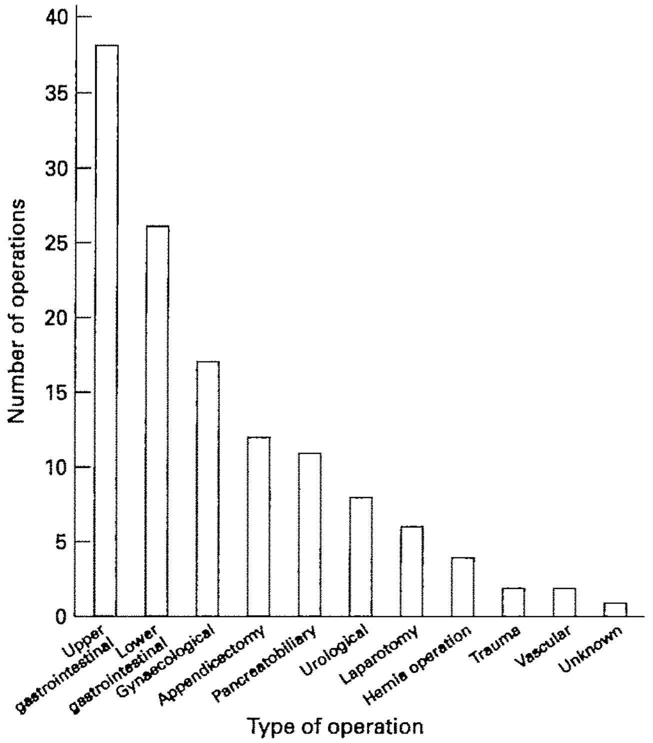


Fig. 2 Total number of procedures of each type before the first admission for obstruction (59 patients, 122 procedures)

Time to presentation with adhesional obstruction

The mean time to presentation in 31 patients with a single previous operation was 8·9 years (range 11 days to 34·7 years) with 26 per cent presenting within 1 year and 48 per cent presenting within 5·5 years.

Type of treatment for obstruction

Thirty-three patients (56 per cent) were successfully treated conservatively on their first admission. It is assumed that any patient exhibiting symptoms or signs of impending bowel ischaemia or peritonitis was treated operatively. There was no significant difference in the patients' subsequent clinical course whether they were treated conservatively or surgically (i.e. number of subsequent admissions or the type of treatment required during each of these admissions). The results suggest that the type or frequency of treatment has no influence on the likelihood of developing further episodes of obstruction (*Tables 2* and *3*). *Fig. 3* is a flow chart which indicates the proportion of patients passing from one form of treatment to another. There was no significant difference in the outcome of patients treated conservatively compared with those treated surgically ($P > 0\cdot2$). Similarly, there was no difference in the outcome of surgically treated patients receiving adhesiolysis or resection ($P > 0\cdot2$).

Length of stay

The length of stay for each conservative admission varied from less than 24 h to 39 days (median 6 days; 57

episodes). The operative admissions varied from 2 to 47 (median 11) days (29 episodes). This difference was statistically significant ($P < 0·001$).

Hypothetical cost of managing adhesions

The potential cost of managing 100 patients was calculated up to the point of the third admission for adhesional small bowel obstruction. This calculation was based on the cost of occupying a bed and of a laparotomy at 1996 prices. These were £135·81 and £470·92 respectively. As the median stay for conservative treatment was 6 days, the median cost would be £814·86. The median cost of one operative stay would be £1964·83 (median stay of 11 days and one laparotomy). Using data from the study a mean percentage of individuals passing from an admission for obstruction to either no further admission, a further conservatively managed admission or a further operatively managed admission was calculated up to the third hypothetical admission (*Fig. 4*).

Table 2 Treatment at each successive admission for adhesional obstruction

No. of patients	Admission 1	Admission 2	Admission 3	Admission 4
Conservative	33	16	9	7
Operative	26	8	5	1
Total	59	24	14	8

There was no statistically significant difference in the proportion of conservative *versus* operative admissions between the different admissions

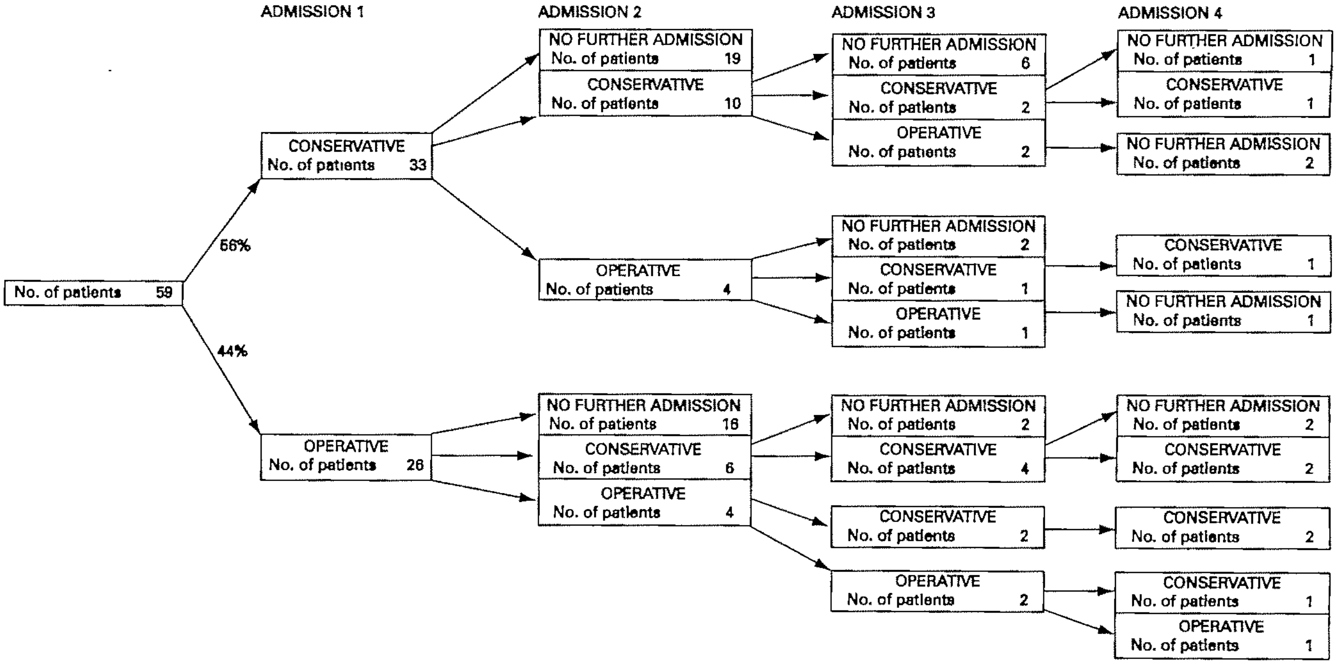
Table 3 Outcome after each admission for adhesional obstruction

	Admission 1	Admission 2	Admission 3	Admission 4
Further admissions	35	10	6	2
No further admissions	24	14	8	6
Total	59	24	14	8

Discussion

This retrospective cross-sectional study has attempted to elucidate the natural history of postoperative adhesional obstruction. ICD codes were used to identify patients treated for adhesional obstruction using information from case notes of patients admitted in the years 1990–1996. The fact that only 59 (33·7 per cent) of 175 cases were correctly coded as having adhesional obstruction should sound a note of caution for any study where these codes are used as a form of case identification. To remove the possibility of including non-adhesional cases of obstruction (e.g. cancer) great care was taken to exclude patients admitted with a primary diagnosis of neoplasia. It is accepted that there may be a small number of individuals who may have had an episode of obstruction due to adhesions during admission for treatment of cancer who are not included in the study, but the aim was to try to study as homogeneous a group as was possible within the confines of the data.

Despite obvious reservations about the retrospective retrieval of information from medical records, the past medical history of all the patients used in this study was recorded. This has the advantage of recalling all previous surgical admissions, including those for obstruction, irrespective of the admitting hospital or even country. This information would require a prospective study with information on which patients were treated at different hospitals. It would be difficult to have a truly 'captive' population.


ADMISSION 1
ADMISSION 2
ADMISSION 3
ADMISSION 4
No. of patients 59
56%
44%
CONSERVATIVE No. of patients 33
OPERATIVE No. of patients 26
NO FURTHER ADMISSION No. of patients 19
CONSERVATIVE No. of patients 10
OPERATIVE No. of patients 4
NO FURTHER ADMISSION No. of patients 16
CONSERVATIVE No. of patients 6
OPERATIVE No. of patients 4
NO FURTHER ADMISSION No. of patients 6
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NO FURTHER ADMISSION No. of patients 2
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CONSERVATIVE No. of patients 2
CONSERVATIVE No. of patients 2
CONSERVATIVE No. of patients 1
OPERATIVE No. of patients 1

Fig. 3 Flow chart showing progress of each patient in the study up to the fourth obstructive episode

Menzies and Ellis' prospective study[3] indicated that while most adhesional obstruction occurs within 10 years (59 per cent by 5 years and 79 per cent by 10 years) there is no time limit as to when a patient may suffer an episode of obstruction. The present study is in agreement with this. The mean time to presentation was 8·9 years with 26 per cent presenting within 1 year and 48 per cent presenting within 5·5 years. However, one patient presented with adhesional obstruction 35 years after an appendicectomy.

The operation types most likely to be followed by episodes of adhesional obstruction were those in the upper gastrointestinal category, followed by lower gastrointestinal procedures if all patients were included. However, if just the patients who had undergone a single procedure before an obstruction-related admission are considered the most common causative operation was of a lower gastrointestinal nature. It is not clear if this is a true reflection of the propensity to form adhesions after these types of operation or whether it is merely a manifestation of the frequency of the performance of these operations. Most admissions for adhesive obstruction occurred after a single previous operation and if this was treated by surgery (either resection or adhesiolysis) the length of stay was significantly longer (median 5 days, $P < 0.001$) than that for those treated conservatively. Interestingly, the type of treatment did not appear to influence how likely it was for the patient to represent with a further episode, nor did it become more likely for the patient to require either surgery or conservative treatment on subsequent admissions.

As the proportion of patients treated operatively or conservatively did not vary significantly between the first and third admission for adhesional obstruction, a

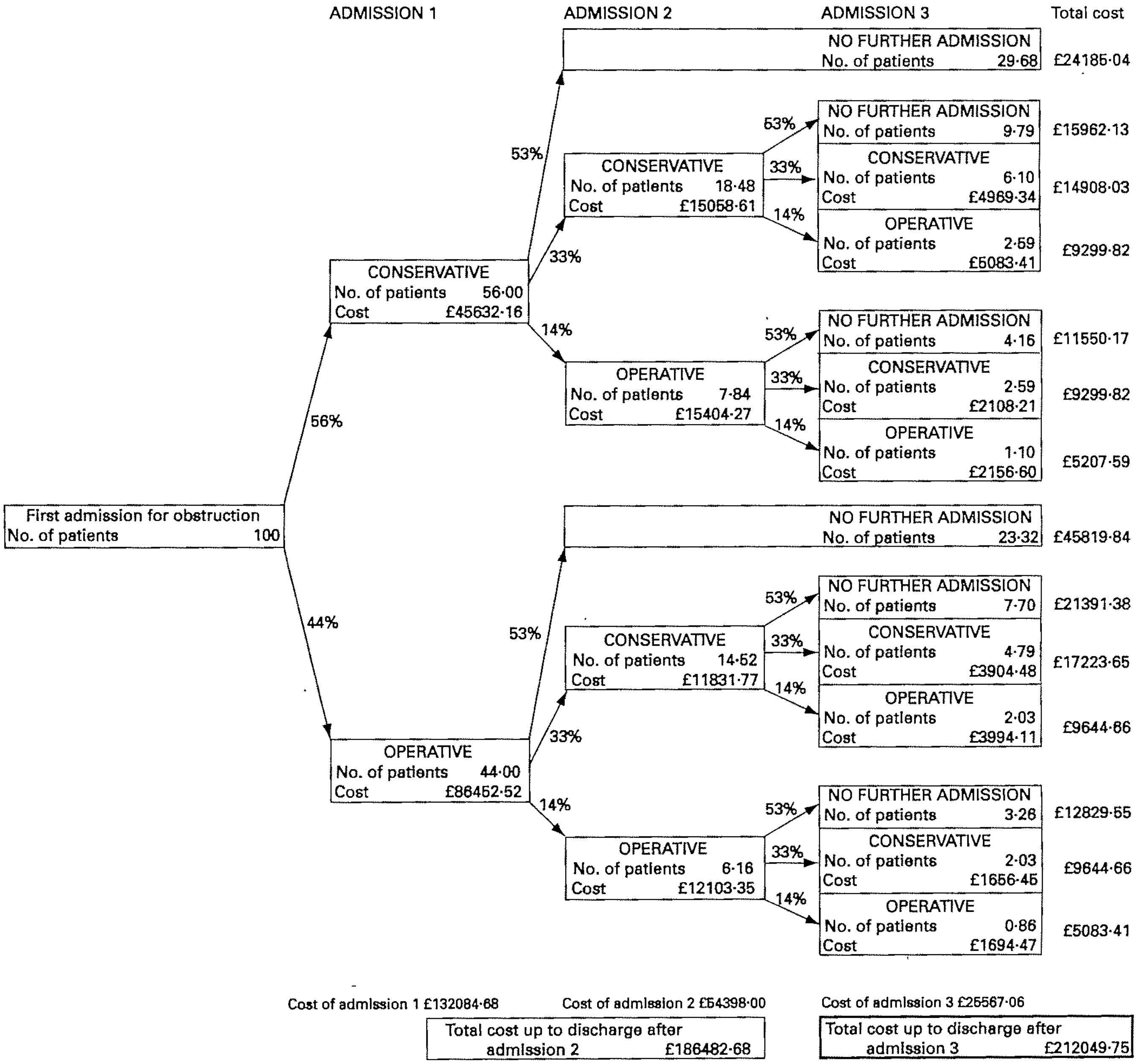

Fig. 4 Hypothetical cost of managing 100 patients up to the third admission for obstruction

standardized percentage of patients could be incorporated into a theoretical flow chart to allow for calculating potential costs of treatment to a number of patients (*Fig. 4*). This type of modelling does not suggest that all patients can be treated in a standardized manner as each individual requires proper assessment. It could be used to assess the potential impact of new treatment strategies for adhesional problems such as the use of laparoscopy and minimally invasive techniques to reduce *de novo* adhesion formation[4]; local enhancement of plasminogen-activating activity to reduce the organization of fibrinous deposits and the formation of permanent fibrous adhesions[5]; and the use of hyaluronidase which does not appear to reduce adhesion formation significantly on its own[6–8] but may be a useful adjunct to surgery when combined with a physical barrier such as methylcellulose (Seprafilm/Sepracoat, Genzyme BV, The Netherlands)[9,10].

In conclusion, this study suggests that the type of treatment for adhesional obstruction does not influence the frequency nor the type of treatment required in subsequent admissions for the same problem.

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Erratum

This abstract was erroneously omitted from the Eurosurgery '98 issue (*Br J Surg* 1998; 85, Suppl. 2) and should have appeared on page 201 in the section entitled *Stomach*. The publishers apologize for this omission.

Lymphadenectomy for carcinoma of the stomach middle third

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This procedure consists in a lymphadenectomy of the I, II, III and IV level nodes. A very extended Kocher's manoeuvre allows a para-aortic dissection of the inferior mesenteric artery to the superior margin of the left renal vein.

Splenectomy with dissection of the splenic artery on the superior edge of the pancreas downstream from the origin of the great pancreatic artery and removal of the splenic artery nodes upstream allow the execution of a complete lymphadenectomy of the splenic artery and hilum according to the 'pancreas preserving' technique.

After mobilization of the pancreas a lateroaortic lymphadenectomy, performed above the left renal vein, is possible. This type of extended lymphadenectomy is indicated in T2b/T3 and/or N2+ carcinomas.

British Journal of Surgery 1998, 85, 1299–1304

British Association of Endocrine Surgeons Abstracts

The following abstracts were presented at the British Association of Endocrine Surgeons meeting held in Sheffield on 8 May 1998. *The British Journal of Surgery* prize was awarded to the abstract entitled 'Fibroblast growth factor receptor type 1 expression in secondary hyperparathyroidism' by D. H. Markham, L. A. Maille, T. Lai, J. R. Farndon and J. M. P. Holly.

Supernumerary ectopic hyperfunctioning parathyroid gland in surgery for sporadic primary hyperparathyroidism

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Background Performed by experienced operators, surgery for sporadic primary hyperparathyroidism (SpHPT) is successful in 95–98 per cent of patients. A supernumerary ectopic hyperfunctioning gland is a major cause of surgical failure.

Methods In a series of 1200 consective patients, six (0·5 per cent) had a supernumerary hyperfunctioning gland in a major ectopic location. No localization studies were performed before initial surgery. One patient was cured at the first exploration. Five other patients underwent localization studies before reoperation for persistent disease. The fifth ectopic parathyroid gland was correctly located in all five patients: ultrasonography, one of five; computed tomography, three of five; TC-Smibi, three of five; selective venous sampling, four of four. Intraoperative measurement of parathyroid hormone (PTH) was performed and was conclusive in two patients.

Results Five of the six patients underwent a second ($n = 3$) or third ($n = 2$) operation. The fifth gland was associated with multiple gland disease in four patients: a double adenoma (one patient) or hyperplastic glands (three). The others presented at initial surgery with four normal glands. The supernumerary ectopic hyperfunctioning gland was located deep within the anterior mediastinum in five and within the carotid sheath in one. This gland was removed transcervically in five patients, but required a sternotomy in one. With a mean follow-up of 6 years, all patients are cured biochemically.

Conclusion The low frequency of a supernumerary ectopic hyperfunctioning parathyroid gland in SpHPT does not require the routine use of preoperative localization studies and intraoperative measurement of PTH at initial bilateral cervicotomy.

Ceramides modulate cytoplasmic calcium and secretion in human parathyroid cells

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Background Ceramides have emerged as important regulators of cell proliferation and function. In bovine parathyroid cells, high extracellular calcium ($[\mathrm{Ca}^{2+}]$ext) activates the sphingomyelin pathway, i.e. the endogenous enzymatic cascade which generates ceramides and sphingosine from sphingomyelin. This study explored the effects of synthetic ceramides on intracellular calcium concentration ($[\mathrm{Ca}^{2+}]$i) and secretion from human parathyroid cells.

Methods Cells from parathyroid adenomas removed from five patients with primary hyperparathyroidism were dispersed and cultured on Pronectin F-coated glass coverslips. Quantitative fluorescent microscopy in Fura2/AM-loaded cells was used to measure $[\mathrm{Ca}^{+}]$i from the ratio of fluorescence intensity at 340 and 380 nm. Laser scanning microscopy (Leica TCS, Kripton/argon laser, 0·5-μm sections) was used to monitor the intracellular distribution of a fluorescent ceramide analogue (C5-BODIPY; Molecular Probes) and the secretion-coupled uptake of FM1–43 fluorescent dye.

Results After addition of C2-ceramide (*N*-acetyl-D-*erytro*-sphingosine; Calbiochem) 10 μmol/l 37 of 55 cells showed a rapid increase in $[\mathrm{Ca}^{2+}]$i to a peak three times above basal levels attained within 6 s. This effect was due to release of calcium from intracellular stores with no calcium entry from extracellular medium. C2-responsive cells had a smaller/absent $[\mathrm{Ca}^{2+}]$i response to subsequent stimulation with neomycin 1 mmol/l, a calcium receptor agonist. These responses appeared to be specific to C2 since a larger analogue, C6-ceramide (*N*-hexanoyl-D-*erytro*-sphingosine; Calbiochem), did not affect basal levels of $[\mathrm{Ca}^{2+}]$i nor the responsiveness to stepping $[\mathrm{Ca}^{2+}]$ext and to neomycin. C5-BODIPY generated intense perinuclear fluorescence, suggesting targeting of the Golgi apparatus. A step in $[\mathrm{Ca}^{2+}]$ext from 3·0 to 0·5 mmol/l induced a rapid uptake of FM1–43 on the plasma membranes followed by internalization of the dye (corresponding to exocytosis and endocytosis respectively). Cells preincubated with C5-BODIPY showed no subsequent FM1–43 uptake in response to a decrease in $[\mathrm{Ca}^{2+}]$ext, suggesting that ceramides act as an inhibitor of exocytosis/endocytosis events in parathyroid cells.

Conclusion These data suggest that endogenous generation of ceramides has the potential to modulate basal $[\mathrm{Ca}^{2+}]$ext in human parathyroid cells.

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Fibroblast growth factor receptor type 1 expression in secondary hyperparathyroidism*

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Background Fibroblast growth factors (FGFs) have been implicated in the pathogenesis of primary parathyroid hyperplasia in patients with multiple endocrine neoplasia type 1 and in the proliferation of cells from the rat parathyroid cell line PT-r. Messenger RNA for FGFs and the FGF receptor type 1 (FGFR-1) has been detected in hyperplastic parathyroid tissue. Alterations in receptor levels caused by the biochemical abnormalities of renal failure such as hypocalcaemia may be important in the mediation of parathyroid growth in patients who develop secondary hyperparathyroidism (2°HPT). The aim of this study was to develop systems to establish the presence of the FGFR-1 protein and monitor the effects of alterations in calcium environment on expression of FGFR-1.

Methods Parathyroid tissue removed from patients with 2°HPT due to renal failure was grown in explant culture for 48 h in media with varying concentrations of calcium. Frozen sections of this tissue and archival paraffin sections of parathyroid tissue from patients with 2°HPT were stained by immunohistochemical methods with a polyclonal antibody to amino acids 808–822 of the carboxy terminus of the FGFR-1 precursor. Tissue from these patients was also homogenized in a lysing buffer and analysed by Western immunoblot following 8 per cent sodium dodecyl sulphate–polyacrylamide gel electrophoresis under denaturing and reducing conditions. Using the same antibody, chemiluminescence techniques were employed to give a semiquantitative measure of the FGFR-1 in the cell lysates.

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*Winner of the *British Journal of Surgery* Prize for the best paper presented by a surgical trainee.

Results Cytoplasmic expression of FGFR-1 in all glands was demonstrated by immunohistochemistry. Western blotting with the same antibody to FGFR-1 gave a clear band at 48 kDa representing one of the isoforms of this highly variably spliced receptor. The presence of the FGFR-1 in significant amounts in parathyroid cells from patients with 2°HPT indicates that it may be significant in mediating parathyroid growth in hyperplasia caused by the biochemical abnormalities of renal failure.
Conclusion The establishment of a novel culture technique followed by the use of methods to detect the presence of FGFR-1 allows the role of the receptor to be investigated in the pathogenesis of parathyroid hyperplasia in 2°HPT.

Endoscopic parathyroidectomy using a gasless procedure

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Background Endoscopic procedures may be particularly suitable because parathyroid adenomas are usually of a small size. Preoperative localization of parathyroid lesions and intraoperative quick parathyroid hormone assay (iQPTHa) may allow a targeted parathyroidectomy.
Methods Thirty-three consenting patients with primary hyperparathyroidism were selected to undergo endoscopic parathyroidectomy on the basis of the following criteria: preoperative echographic diagnosis of a single adenoma, no evidence of nodular goitre and no previous neck surgery. There were 27 women and six men of mean(s.d.) age 54·5(14·4) years. Mean follow-up was 6·8 (range 1–12) months. Under general endotracheal anaesthesia, the patient is placed in a supine position and a 1·5-cm incision is made above the sternal notch, where a 12-mm trocar is inserted under the strap muscles on the side of the suspected adenoma. Carbon dioxide is insufflated for no longer than 3–4 min to anatomically dissect the thyrotracheal groove. After removing the trocar the procedure is then carried out on a gasless basis, using only the anterior incision and one additional 2-mm needlescopic lateral access.
Results Thirty-three parathyroid adenomas (confirmed by histological examination) were removed from 33 patients. The iQPTHa always demonstrated a decrease of more than 50 per cent of parathyroid hormone plasma levels. Mean operative time was 65 (range 30–180) min. Neither pneumomediastinum nor emphysema of the neck occurred. Serum calcium was normal in all patients. Cosmetic results were considered excellent by the patients.
Conclusion Endoscopic parathyroidectomy is a feasible and safe procedure in a selected series of patients. The gasless approach seems to offer the advantages of avoiding metabolic and cosmetic negative affects linked to a long carbon dioxide insufflation. It does not influence the duration of operation.

Parathyromatosis as a rare cause of recurrent and persistent hyperparathyroidism

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Background Parathyroid cells retain a remarkable ability to grow and function following transplantation into muscle or subcutaneous fat. Parathyromatosis, i.e. the finding of multiple nests of parathyroid tissue, may occur following parathyroid surgery or rarely as an embryological abnormality at initial operation. This study reviews the experience of parathyromatosis at one centre over a 27-year period.
Methods The records of all patients with recurrent or persistent hyperparathyroidism were reviewed. Patients with more than five sites of parathyroid tissue at reoperation were included.
Results There were seven women and one man. Seven patients were referred from other centres. Causes of hyperparathyroidism were renal failure (six), adenoma (one) and multiple endocrine neoplasia I (one). Initial procedures were subtotal parathyroidectomy (six) and multiple biopsies with removal of a normal gland (two). Since the original operations, 59 subsequent procedures have been performed, including seven thyroid lobectomies, seven modified neck dissections and five median sternotomies. Five patients experienced improvement in hypercalcaemia following initial reoperation. No long-term complications were encountered. All eight patients continue to have hyperparathyroidism.
Conclusion Parathyromatosis is extremely rare, occurring most frequently in patients with secondary hyperparathyroidism. Patients are difficult to cure and tumours are found throughout the neck and mediastinum. The aetiology of parathyromatosis is unknown.

Subtotal parathyroidectomy *versus* total parathyroidectomy with autotransplantation

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Background Outcome after subtotal parathyroidectomy (sPTX) and total parathyroidectomy with autotransplantation (PTX + AT) was compared.
Methods Thirty patients undergoing either PTX + AT ($n = 11$) or sPTX ($n = 19$) have been reviewed. The surgery was performed by a single surgeon between 1990 and 1997.
Results Permanent hypoparathyroidism was reported in none of the patients who underwent sPTX and in four patients who underwent PTX + AT. Although no reoperations were necessary, postoperative parathyroid hormone levels were frequently raised in patients from both groups. Postoperative hypocalcaemia occurred with a greater frequency following PTX + AT (ten of 11) than sPTX (ten of 19). Both procedures were effective at normalizing serum calcium and alkaline phosphatase in the majority of patients, but serum phosphate rarely normalized following PTX + AT. Eighteen months after parathyroidectomy, mean serum phosphate levels were 1·71 and 1·04 mmol/l in patients who underwent PTX + AT and sPTX respectively. Calcium supplements were required in higher doses and vitamin D analogues were required more frequently following PTX + AT than sPTX.
Conclusion Subtotal parathyroidectomy is the surgical operation of choice in patients with tertiary hyperparathyroidism.

Treatment of an insulinoma in pregnancy with guar gum

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Background Insulinoma diagnosed in pregnancy is very rare. There are 14 cases in the literature. A 40-year-old Jehovah's witness who was 12 weeks pregnant presented with the signs and symptoms of hyperinsulinism (blood sugars below 2·1 mmol/l and inappropriate insulin and C-peptide levels).
Methods Magnetic resonance imaging of the abdomen showed a well circumscribed 3-cm tumour in the tail of the pancreas. The symptoms were such that she needed intravenous glucose later replaced by regular 2-hourly feeding. Standard management with dizoxide was not used because of the documented risk of foetal abnormalities in animals. The 2-hourly feeding became intolerable with concerns about the effects of hypoglycaemia on the foetus. A novel regimen of oral guar gum 5 g three times a day was instituted. This high molecular weight polysaccharide (Galactomanan) increases the gastric transit time and slows the absorption of carbohydrates.
Results The guar gum (with three regular meals a day) resulted in complete control of the hypoglycaemia. At term an elective caesarian section was performed with a living infant delivered with a rare abnormality in chromosome 4. Before laparotomy superselective angiography with calcium stimulation was performed confirming the presence of an insulinoma in the tail of the pancreas. At laparotomy a benign insulinoma was removed

by enucleation. After operation the insulin and blood sugar levels were within the normal range.
Conclusion Guar gum should be considered for the management of insulinoma in pregnancy where other therapies may produce foetal abnormalities and where it is crucial that blood sugars are kept within the normal range.

Laparoscopic procedures for patients with large or potentially malignant adrenal tumours

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Background Laparoscopic adrenalectomy (LA) is safe and effective for small, benign, functioning tumours. The aim of this study was to evaluate the results of LA for large or potentially malignant tumours.
Methods From June 1994 to December 1997 LA was performed on 113 occasions in 109 patients. A transperitoneal flank approach in the lateral decubitus position was used. Initially indications for LA were limited to small (less than 4 cm), benign, functioning tumours (group 1; $n=78$): aldosteronomas (50), Cushing's syndrome (22), pheochromocytomas (six). Progressively based on an increasing experience, LA was also proposed for tumours larger than 4 cm or potentially malignant (group 2; $n=35$): Cushing's syndrome (five), pheochromocytomas (12), non-functioning tumours (18). Preoperative demonstration of invasive extra-adrenal carcinoma remained an absolute contraindication for LA.
Results Results of surgery were compared between the two groups.

	Group 1	Group 2
Mean tumour size (mm)	20·8	52·5
Mean operative time (min)	128	135
Malignancy	0	3
Complications (%)	9	3
Conversions (%)	5	6

The endocrinopathy was cured in all patients and no recurrences were observed.
Conclusion LA can be used for large (less than 15 cm) or potential malignant tumours provided that preoperative investigations have not demonstrated invasive carcinoma. The procedure should be converted to open if local invasion is observed at the beginning of the operation.

Indication for adrenalectomy in patients with adrenal lesions and a history of previous carcinoma

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Background Hormone inactive adrenal tumours less than 3 cm in diameter do not require surgery because of the extremely low probability of malignancy. The aim of this study was to investigate if this strategy should apply to patients with a previous history of a carcinoma.
Methods From 1992 to 1997 73 patients with adrenal tumours were investigated.
Results In 49 patients (67 per cent) the tumour was benign. Fifteen patients (21 per cent) presented with adrenal carcinoma. Nine of the patients with adrenal tumours (12 per cent) were treated for carcinoma not related to adrenal (bronchus, two; colon, one; uterus, two; breast, one; kidney, one; lymphoma, one; melanoma, one) in the past. In all nine patients histological examination of the adrenal tumour revealed metastases of the primary carcinoma. Six patients were asymptomatic and three were suffering from abdominal pain. The period from the primary tumour diagnosis to adrenal tumour removal was between 3 months and 5 years. The diameter of the adrenal metastases was between 4 and 19 cm.
Conclusion In all patients with adrenal tumours and a history of carcinoma, adrenalectomy should be performed independently of the tumour size and hormone activity. These adrenal tumours are most likely metastases of the primary carcinoma.

Essential hypertension as a cause of persistent hypertension after unilateral adrenalectomy for primary aldosteronism

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Background Hypertension persists after operation in 30–50 per cent of patients after successful surgical correction of primary aldosteronism. The aim of this study was to determine factors influencing long-term outcome of blood pressure after unilateral adrenalectomy in patients with primary aldosteronism defined as spontaneous hypokalaemia, hyperaldosteronism and low plasma-renin activity.
Methods Records of 91 patients operated between 1970 and 1996 in one institution were reviewed. Patients were distributed in two groups according to whether blood pressure was normal (World Health Organization criteria) or not at the time of the study. Clinical and biochemical factors, surgical approach and pathological findings were compared. Patients with persistent hypertension underwent further investigation.
Results Primary aldosteronism was cured in all patients. Blood pressure was normal in 53 patients (58 per cent; mean follow-up 75 months) and improved in 38 (42 per cent; mean follow-up 67 months). Persistent hypertension was correlated with known duration of hypertension ($P=0·036$, non-paired t test), degree of preoperative systolic ($P=0·0096$) and diastolic ($P=0·0082$) blood pressure increase. The preoperative response to spironolactone was predictive of hypertension cure ($P=0·04$, χ^2 test). Sex, age, pathological findings and surgical approach were not predictive of outcome. No biochemical recurrence occurred in those with persistent hypertension, but plasma renin activity remained in the low range.
Conclusion Unilateral adrenalectomy allows cure of hypertension in most patients with a unilateral excessive source of aldosterone secretion. In patients with essential hypertension and primary aldosteronism, surgical treatment improves blood pressure. Early surgical intervention in patients with a good response to spironolactone results in a favourable outcome whatever the pathological findings might be.

Laparoscopic adrenalectomy for phaeochromocytoma

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Background The authors' experience with laparoscopic adrenalectomy for phaeochromocytoma was reviewed.
Methods Fifteen attempted laparoscopic adrenalectomies for phaeochromocytoma with one conversion are reported. The mean age of the patients was 50 (range 29–84) years.
Results Tumour size ranged from 1·5 to 8 cm in diameter. Ten lesions were left-sided and five right-sided. Operating time was 105–240 (mean 185) min. Blood loss was minimal, less than 500 ml, except for the patient who required conversion (2000 ml). Hospital stay ranged from 2 to 6 (mean 3) days. Two patients experienced morbidity, one urinary tract infection and one port-site infection.

Conclusion These results compare favourably with a recently reported series of patients undergoing subcostal 'open' surgery for phaeochromocytoma.

Modified radical neck dissection improves prognosis in patients with papillary carcinoma of the thyroid

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Background The aim of the study was to ascertain whether modified radical neck dissection offers a survival advantage for subsets of patients with papillary cancer of the thyroid.
Methods Between 1946 and 1991, patients with papillary cancer whose primary tumour was 1 cm or larger and who were curatively treated were studied. Of 2859 patients, 72·1 per cent underwent modified radical neck dissection, 8·5 per cent underwent partial node excision and 19·4 per cent underwent no node excision.
Results Univariate analysis revealed some subsets of patients who benefited from modified radical neck dissection. Multivariate analysis revealed that sex ($P < 0{\cdot}001$), age at the time of operation ($P < 0{\cdot}001$), size of the primary tumour ($P < 0{\cdot}001$), extrathyroidal invasion ($P < 0{\cdot}001$) and the presence of nodal metastasis ($P < 0{\cdot}015$) are significant risk factors.
Conclusion Patients with nodal metastasis, patients in whom the primary tumour invades beyond the thyroid capsule, and women older than 60 years can benefit from modified radical neck dissection.

Comparison of thyroid peroxidase and dipeptidyl-aminopeptidase in the diagnosis of malignancy of thyroid nodules

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Background Loss of immunoreactivity of thyroid peroxidase (TPO), detected with antibody Mab 47 in malignant thyroid cells, can be used to improve the accuracy of thyroid fine-needle aspiration cytology (FNAC). The enzyme dipeptidyl-aminopeptidase (DAP4), abnormally expressed by malignant thyroid cells, may be of similar value. This study compared the value of these markers in the cytodiagnosis of thyroid cancer.
Methods FNAC samples were stained with Giemsa (GS) and subjected to TPO immunocytochemistry and DAP4 histochemistry. These were compared with the histological diagnosis of 496 benign and 146 malignant thyroid nodules. GS-stained samples were classified as benign (B) *versus* suspicious or malignant (M). The TPO stain was expressed as the percentage of positive cells and DAP4 as a score ranging from 0 to 12. Malignancy was expected for TPO staining less than 80 per cent or a DAP4 score of 6 or more.
Results A correct diagnosis of malignancy was achieved in 88 per cent of cancers with GS, 98 per cent with TPO and 82 per cent with DAP4. False negatives were 11 papillary and six follicular cancers with GS; two papillary and one follicular lesions with TPO; and four medullary, four oncocytic, eight papillary, six follicular and four others with DAP4. The specificity of the three methods was respectively 76, 81 and 91 per cent. The association of TPO staining of 20 per cent or less and a DAP4 score of 12 had an absolute predictive value. The best negative predictive value of 100 per cent was obtained by the association GS = B, TPO staining 80 per cent or less and DAP4 score 0. The best general performance was obtained when all samples with GS = M or TPO 50 per cent or less or TPO 80 per cent or less and DAP4 score equal to or less than 4 or TPO 80 per cent or less were considered as malignant. The sensitivity for cancer was then 98 per cent and the specificity 84 per cent.
Conclusion TPO immunodetection and DAP4 histochemistry are both powerful markers for the cytodiagnosis of thyroid cancer. TPO immunodetection alone is more important than the other methods but the best results are obtained when combined with GS and DAP4 activity.

Medullary thyroid carcinoma cell line rMTC6–23 expresses V_1-vasopressinergic receptors

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Background Human medullary thyroid carcinomas are a rare source of ectopic adrenocorticotrophic hormone (ACTH) secretion. In such tumours, secretion of calcitonin and ACTH responds to changes in plasma calcium levels and vasopressin. This study explored whether a medullary carcinoma cell line (rMTC6–23 clone, ECCAS) expresses functional vasopressinergic receptors.
Methods rMTC6–23 cells were cultured in DMEM medium on Matrigel-coated glass coverslips. Quantitative fluorescent microscopy in Fura2/AM-loaded cells was used to measure intracellular calcium concentrations ($[Ca^{2+}]i$) from the ratio of fluorescence intensity at 340 and 380 nm. Cells were tested with $[Arg^8]$vasopressin (AVP) and with an agonist of V_1-vasopressinergic receptors ($[Phe^2, Orn^8]$-vasopressin, POVT).
Results Incubation of rMTC6–23 cells with high concentrations of AVP (10^{-5}–10^{-6} mol/l) induced a rapid rise in $[Ca^{2+}]i$ with a peak attained within 30 s and returning to basal level within the next 2 min despite the continuous presence of the agonist and of extracellular calcium. These responses were not repeatable within 15–30 min, suggesting rapid desensitization of AVP receptors. Low concentrations of AVP (10^{-9}–10^{-8} mol/l) induced oscillations of $[Ca^{2+}]i$ with high amplitude (twofold to threefold above basal level) and a frequency of approximately 0·3–1 per min. The effect of AVP on $[Ca^{2+}]i$ was dose dependent over a range of 10^{-9}–10^{-6} mol/l, with a higher percentage of cells responding to increasing concentrations of AVP. Addition of the V_1-agonist POVT (10^{-9}–10^{-6} mol/l) reproduced the effects of AVP on $[Ca^{2+}]i$.

Bone marrow staining for disseminated tumour cells in patients with medullary thyroid carcinoma

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Background Persistence of hypercalcitonaemia after surgery for medullary thyroid carcinoma (MTC) is frequent despite extensive lymph node dissection. Sophisticated imaging technologies often fail to trace distant metastases. The role of the bone marrow as a potential site for occult metastases is unclear.
Methods Between April and October 1997, bone marrow aspirates were obtained from 21 consecutive patients undergoing repeat lymph node dissection for suspected or proven MTC lymph node metastases. After preparation, 19 samples were of sufficient quality for immunostaining.
Results In six of 19 patients, single cells stained positive for calcitonin. No clusters of immunopositive cells were noted. Unlike pT category, lymph node status (pN_{1b}) correlated with positive bone marrow aspirates. One-third of patients with positive bone marrow aspirates revealed distant metastases, which were confirmed histologically. Basal calcitonin levels were raised in four of six patients after repeat surgery. On pentagastrin stimulation, the fifth patient showed a pathological response, whereas the sixth patient with a normal basal calcitonin level was entirely unresponsive to stimulation.
Conclusion Dissemination of tumour cells to the bone marrow accounts for raised serum calcitonin levels in a subset of patients. Bilateral lymph node involvement was a major risk factor for tumour cell spread to the bone marrow. In those with positive bone marrow aspirates it might be wise to limit the extent of lymph node dissection because of the impossibility of tumour eradication.

Resternotomy and repeat lymph node dissection in patients with advanced medullary thyroid carcinoma

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Background In patients with medullary thyroid carcinoma (MTC), clinical experience of repeat mediastinal lymph node dissection is limited.

Methods Between January 1995 and March 1997, seven patients with postoperative hypercalcitonaemia were subjected to resternotomy and repeat mediastinal lymph node dissection.

Results At primary surgery, all patients exhibited positive cervial lymph nodes (pN_1). A mean of six of 22 excised cervical and three of 11 resected mediastinal lymph nodes were involved. At reoperation, a mean of six of 24 removed cervical and four of nine dissected mediastinal lymph nodes were positive on histopathology. A substantial fraction of positive lymph nodes was excised from anatomical regions inaccessible through a purely cervical or partial sternotomy approach. Because of selective lymph node dissections and partial sternotomies, only 22 of 46 cervical and 11 of 20 mediastinal lymph nodes had been removed at primary surgery. Serum calcitonin fell after operation by 34 per cent, but was not entirely converted to normal, suggesting distant micrometastases. There were no deaths. Morbidity included two patients with hypoparathyroidism, a transitory palsy of the recurrent nerve, a lymphatic fistula that closed spontaneously on total parenteral nutrition, and bleeding in a patient with hepatitis C-related liver cirrhosis.

Conclusion When mediastinal lymph node metastases are present, repeat lymph node dissection, which is reasonably safe in experienced hands, is indicated to achieve local tumour control.

Minimalist approach to the investigation of thyroid swellings: prospective analysis of 1000 consecutive referrals to a surgical thyroid clinic

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Background A policy of a conservative approach to the investigation of thyroid swellings was assessed. The clinical outcome in 1044 consecutive patients referred to a dedicated surgical thyroid clinic serving a population of 450 000 was studied prospectively between 1992 and 1997. Data on mode of presentation, clinical features, investigations, operation and pathology were recorded.

Methods Some 63 patients with Graves disease were referred from the medical clinic for consideration of surgery, of whom 43 underwent subtotal or total thyroidectomy. The remainder presented with a presumed thyroid swelling. There were 126 men (13 per cent) and 855 women (87 per cent). Routine investigation comprised estimation of thyroid function, thyroid autoantibody titres and fine-needle aspiration cytology (FNAC) for patients with isolated or dominant thyroid swellings and some multinodular or generalized swellings.

Results Some 74 per cent of patients underwent FNAC; 1512 aspirations were performed on 729 patients: 290 (40 per cent) had only one, 220 (30 per cent) had two, 95 (13 per cent) had three and 124 (17 per cent) had more than three. The requirement for repeated FNAC results in an increase in return visits but nevertheless FNAC remains the most important and, for the majority of patients, the only investigation. Ultrasonography was ordered in only three patients, and radiographs of the chest and thoracic inlet performed at the clinic were the only other investigation. Some 378 patients underwent an operation; there were 171 non-neoplastic lesions, 136 follicular neoplasms of which 27 were malignant, 26 papillary, three medullary, one anaplastic and one metastatic carcinomas, eight lymphomas and 12 miscellaneous lesions. The reasons for the decision to operate were recorded prospectively. When clinical suspicion was the sole indication for operation in 45 patients with no cytological or other evidence, there were 19 follicular neoplasms (one malignant), two papillary carcinomas and two lymphomas.

Conclusion A population-based study such as this provides information on which to base recommendations for service provision.

Correlation between tumour size and results of [^{131}I]metaidobenzylguanidine scintigraphy in patients with phaeochromocytoma and paraganglioma

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Background [^{131}I]metaidobenzylguanidine scintigraphy (^{131}I MIBG) detects chromaffin tumours with a high specificity but its sensitivity remains limited. In this study the influence of tumour size on the results of ^{131}I MIBG in patients with phaeochromocytoma and paraganglioma was investigated.

Methods The records of 104 patients operated on for chromaffin tumours who had preoperative ^{131}I MIBG were reviewed. Demographic data, clinical features, biochemical results and pathology of tumours were analysed. The size of the tumour was assessed by the three measured diameters of the specimen and its calculated volume. The univariate relationship between tumour characteristics and the results of ^{131}I MIBG was examined with Mann–Whitney U and/or Fisher's exact tests.

Results Of 119 tumours, 104 (87 per cent) were detected by ^{131}I MIBG. Mean(s.d.) largest diameter and volume of the tumours were 6·0(2·4) (range 0·8–11·5) cm and 68(74) (range 0·2–421) cm^3. Results of ^{131}I MIBG correlated significantly with both the largest diameter of the tumour ($P < 0·01$) and its volume ($P < 0·001$). ^{131}I MIBG was always positive when the volume was above 85 cm^3 ($P < 0·01$). No other criteria correlated with positive ^{131}I MIBG, including pathology or catecholamine secretion pattern.

Conclusion The result of ^{131}I MIBG in patients with chromaffin tumours significantly correlates with the size of the tumour. Tumour size estimated by three-dimensional imaging procedures such as computed tomography and magnetic resonance imaging should be taken into account when interpreting the ^{131}I MIBG scan.

Clinical value of a morphological cytological classification of thyroid nodules

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Background Fine-needle aspiration biopsy (FNAB) of thyroid nodules facilitates the selection of patients for surgery, but the management of follicular nodules (FN) is still a clinical dilemma and histological examination is usually required for an exact diagnosis. In this study the relability of a morphological cytological classification of FN was evaluated.

Methods Some 122 patients with a diagnosis of FN and with histological controls were observed consecutively between 1993 and 1997. All the cytological specimens were classified in three categories according to morphological criteria: thyrocytic hyperplasia without nuclear atypia (THWNA), predominantly follicular lesion (PFL) or follicular lesion with nuclear pleomorphism (FLWNP).

Results Forty-two patients (34·4 per cent) showed THWNA, 66 (54·1 per cent) PFL and 14 (11·5 per cent) FLWNP. The cytological–histological correlation showed a low incidence of neoplasm, either benign or malignant, in the first group (five follicular adenomas, no carcinomas) and a higher rate in the second (24 follicular adenomas, five carcinomas). The highest rate of adenomas and malignancy was found in the third group (six each). The difference between the three groups was statistically significant, considering both the proportion of neoplasms ($P = 0·00003$) and malignancies ($P = 0·08$).

Conclusion These results suggest that this classification could represent a guide for the management of FN. A conservative approach is suitable in those with THWNA; however, because of the risk of malignancy, surgery is advisable in those with PFL and mandatory if there is FLWNP.

Non-invasive imaging of insulinomas and gastrinomas with endoscopic ultrasonography and somatostatin receptor scintigraphy

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Background Classical morphological techniques (computed tomography, magnetic resonance imaging and ultrasonography) are of little value for imaging endocrine duodenopancreatic tumours. Invasive procedures such as intra-arterial stimulation tests are often performed to allow preoperative regionalization of these elusive lesions. Recently, endoscopic ultrasonography (EUS) and somatostatin receptor scintigraphy (SRS) have been introduced for imaging neuroendocrine tumours. This report examines the use of these techniques in patients with insulinoma and gastrinoma.

Methods The records of patients with insulinoma ($n = 19$) or gastrinoma ($n = 17$) and who had preoperative EUS ($n = 29$) and/or SRS ($n = 25$) were reviewed. The clinical and biological diagnosis was confirmed by histology in all cases.

Results The sensitivity and positive predictive value (PPV) of EUS were respectively 75 and 94 per cent for pancreatic tumours (insulinomas and gastrinomas), 83 and 83 per cent for duodenal gastrinomas, and 40 and 75 per cent for gastrin-positive lymph nodes. Overall, EUS was falsely positive in three patients (PPV 88 per cent). In patients with Zollinger–Ellison syndrome, the sensitivity and PPV of SRS were 50 and 100 per cent for pancreatic gastrinomas, and 64 and 90 per cent for duodenal gastrinomas and/or gastrin-positive lymph nodes. Overall, only one false positive was observed with SRS (PPV 92 per cent). SRS demonstrated liver uptake in two of five patients with liver metastases confirmed at surgery. In patients with multiple endocrine neoplasia, neither technique detected all tumours.

Conclusion In patients with sporadic neuroendocrine tumours, EUS can detect with a high predictive value more than 75 per cent of duodenopancreatic lesions and 40 per cent of metastatic lymph nodes. SRS yields similar results for gastrinomas and may detect occult liver metastases. EUS for insulinomas and EUS and SRS for gastrinomas surpass all other non-invasive preoperative imaging procedures and may render invasive procedures unnecessary for most patients.

Evaluation of upper airway obstruction due to thyromegaly

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Background Fifty-one consecutive patients with thyromegaly and symptoms of upper airway obstruction (UAO) were investigated with flow volume loop spirometry (FVL) to determine if this investigation correlated with symptomatology, the effect of surgery and the mass of thyroid removed.

Methods Patients admitted for thyroidectomy with compressive symptoms were investigated with FVL before operation. Following surgery this test was repeated in 22. The FVL parameters were correlated with subjective changes in dyspnoea, choking and stridor, and mass of the thyroid tissue removed.

Results All except three goitres were benign on histological examination and the mean(s.d.) excised weight was 126(93) g. The male:female ratio was 4:47 and the median age was 52 (range 23–77) years. Symptomatically 28 (55 per cent) were improved by surgery; of these, nine had a definitely positive preoperative FVL. Three FVL investigations were uninterpretable.

	Symptomatically improved	No change in symptoms
FVL diagnostic of UAO	9	6
FVL possibly diagnostic of UAO	3	2
FVL	15	13

There was no difference between the paired preoperative and postoperative FVL parameters but correlation of these with mass of thyroid removed was significant before operation for the inspiratory functions PIF50 and PEF50/PIF50 ($P < 0{\cdot}01$, Spearman's rank).

Conclusion This study was not able to identify a convincing advantage to this test.

British Journal of Surgery 1998, 85, 1305–1307

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Laparoscopic drainage of liver abscesses

Sir
We note with interest the experience of Tay *et al.* (*Br J Surg* 1998; 85: 330–2) in the management of liver abscesses in Singapore. The condition is common in the Fiji Islands; we have treated 14 patients in the past 3 months. The abscesses have varied in size between 5 and 12 cm and patients experienced a variable degree of toxicity.

Management has been conservative; all patients were treated with antibiotics. Using an elderly ultrasonography machine many abscesses are aspirated repeatedly. In persistent cases, intralesional antibiotics have been used. In no instance has it been necessary to perform any sort of operative drainage and all patients have left hospital asymptomatic. There has been one death in the past 6 months as a result of diabetic nephropathy. We are surprised at the necessity of undertaking so many operations in Singapore.

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Author's reply

Sir
We agree that conservative methods should be the first line of management. The 36 patients managed interventionally are a small proportion of the total number treated during that period. The majority were successfully treated with antibiotics without the need for surgical intervention.

Image-guided percutaneous drainage was carried out only if the abscess was too large or failed to resolve after an adequate course of antibiotic therapy. As indicated, of the 36 patients managed with percutaneous drainage, 16 procedures were successful. The remaining 20 abscesses did not resolve and underwent laparoscopic drainage based on the indications stated.

Surgical drainage of large liver abscesses is a well documented procedure and we suggest laparoscopic drainage as an alternative to the open procedure.

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Effect of endoscopic sphincterotomy and interval cholecystectomy on late outcome after gallstone pancreatitis

Sir
Of 49 patients undergoing successful endoscopic sphincterotomy alone (*Br J Surg* 1998; 85: 333–6) only one had recurrent pancreatitis. Although it appears that five of 32 patients had recurrent pancreatitis in the group not undergoing endoscopic sphincterotomy, three of these recurrences were in patients without gallbladders, with previous evidence of a normal extrahepatic biliary tree and associated with normal biochemical tests. It is therefore unlikely that these represent gallstone-induced pancreatitis. Furthermore, the 16 patients in group 2 who had definitive therapy in the form of a cholecystectomy should be excluded from comparative analysis. Therefore the comparison evaluating the patients at risk for recurrent gallstone-induced pancreatitis is between one of 49 patients in group 1 and two of 16 in group 2 ($\chi^2 = 3{\cdot}00$, $P = 0{\cdot}15$, Fisher's exact test). The data do not, therefore, sustain the conclusion that endoscopic sphincterotomy reduces significantly the risk of recurrent pancreatitis. As patients had the diagnosis of gallstone-induced acute pancreatitis made on clinical and biochemical criteria without computed tomography it is difficult to be certain what proportion of patients with acute gallbladder pathology were misclassified as acute pancreatitis. There is often a significant overlap between the symptom complex of mild cholecystitis and mild gallstone-induced acute pancreatitis. Clearly, if patients with cholecystitis are grouped together with patients who have true gallstone-induced pancreatitis, there will be an increased requirement for cholecystectomy. This is probably why 31 per cent (20 of 65) of the patients with a diagnosis of gallstone-induced pancreatitis not undergoing routine cholecystectomy subsequently needed surgery which is in contrast to the 4 per cent reported elsewhere[1].

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1 Welbourn CRB, Beckly DE, Eyre-Brook IA. Endoscopic sphincterotomy without cholecystectomy for gallstone pancreatitis. *Gut* 1995; 37: 119–20.

Author's reply

Sir
I appreciate the interest expressed in our article by Dr Praseedom and colleagues. In the results we stated that the overall incidence of recurrent pancreatitis was lower after endoscopic sphincterotomy, but there was no difference between patients who underwent interval cholecystectomy and had had endoscopic sphincterotomy or not. In the discussion we pointed out that some of the recurrent attacks of pancreatitis were probably not of biliary origin. Considering this, and the limited number of patients investigated, we concluded that 'our results do not favour routine endoscopic sphincterotomy in patients with gallstone pancreatitis'. As to the diagnosis of gallstone pancreatitis, all patients were investigated with ultrasonography. The patients included in this study had no ultrasonographic evidence of concomitant acute cholecystitis. I think it unlikely, therefore, that a significant number of the patients had acute gallbladder disease in connection with the acute pancreatitis and that this had any influence on the need for subsequent cholecystectomy.

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Non-operative management of blunt hepatic trauma

Sir

I read with interest the Review by Carrillo *et al.* (*Br J Surg* 1998; 85: 461–8). We have attempted to treat patients with blunt hepatic trauma by conservative means in this institution over the past 11 years. The amount of bleeding intraperitoneally is very difficult to estimate by computed tomography (CT) and I wonder how the authors establish 500 ml of blood as the cut-off point of conservative treatment? I agree with their notion that the most important yardstick for or against non-operative treatment is the haemodynamic state of the patient. Follow-up CT should be reserved to help identify a collection if the patient develops sepsis. The value of CT in determining healing or otherwise is not a cost-effective measure. Most of our patients sustained injuries secondary to motor vehicle accidents. Many do not wear seat belts and this results in major head injury in association with hepatic injury. We have noticed that non-operative treatment can be applied safely to this group as long as brain perfusion and oxygenation is maintained. A word of caution has to be given for patients with multiple trauma and a need for extensive blood transfusion. Excessive transfusion may lead to early coagulopathy and acidosis. Mortality is high in this subset of patients. It may be important to consider early operation and packing if other injuries (major bone fracture, pelvic fracture) necessitate excessive transfusion.

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Author's reply

Sir

Dr El Boghdadly raises some interesting issues. First, in the hands of experienced trauma radiologists, the amount of haemoperitoneum can be calculated with a fair degree of accuracy; however, as stated in our article, it is haemodynamic stability that will indicate the type of treatment rather than radiological findings alone. We could not agree more that there is a very limited role for follow-up computed tomographic studies in these patients and make that point clear when we emphasize that we use it on a selective basis only. Regarding the level of transfusion, we always try to determine what is liver-related and what is not. Early operation, indicated by an increase in requirement of blood transfusion without evidence of active liver haemorrhage is, in general, a bad idea. We try in these circumstances to get an interventional radiologist involved as soon as possible to help determine the source of the haemorrhage as well as control it (see algorithm). More often than not in patients with multiple injuries complex pelvic trauma is the source of bleeding.

We appreciate Dr El Boghdadly's insightful and critical comments and believe that they reinforce the experience described in this Review.

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Changing trends in the management of phaeochromocytoma

Sir

This paper (*Br J Surg* 1998; 85: 117–20) outlines the evolution of adrenal surgery over the 14 years of the study but generally omits the most recent advance: the development of laparoscopic adrenalectomy. The authors believe that 'further experience with laparoscopic excision of phaeochromocytoma is required before its potential can be realized and its limitations recognized'.

Since Gagner described the first laparoscopic adrenalectomy, numerous procedures have been performed and reported in the literature. Gagner *et al.* recently reported a series of 100 laparoscopic adrenalectomies (25 for phaeochromocytoma)[1] concluding that the laparoscopic approach should be the surgical procedure of choice for all benign lesions under 15 cm in diameter[2]. Our experience would corroborate these figures. Indeed, we believe that laparoscopic adrenalectomy for phaeochromocytoma is positively indicated as there is less manipulation of the tumour and metastatic extension of disease can be detected laparoscopically which would be missed via the posterior approach to the adrenal gland.

To entitle this paper as the authors have done and to ignore the most significant change in the management of this disease in recent years leaves a major defect and renders the paper obsolete.

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1 Gagner M, Pomp A, Heniford BT, Pharand D, Lacroix A. Laparoscopic adrenalectomy: lessons learned from 100 consecutive procedures. *Ann Surg* 1997; 226: 238–46.
2 Gagner M, Breton G, Pharand D, Pomp A. Is laparoscopic adrenalectomy indicated for phaeochromocytomas? *Surgery* 1996; 120: 1076–9.

Randomized multicentre trial of the influence of recombinant human erythropoietin on intraoperative and postoperative transfusion need in anaemic patients undergoing right hemicolectomy for carcinoma

Sir

Kettelhack *et al.* (*Br J Surg* 1998; 85: 63–7) did not find a significant variation of haemoglobin level or transfusion rate following preoperative administration of 1500 U/kg of recombinant human erythropoietin (r-HuEPO) in moderately anaemic patients with colonic cancer. This was a similar result to that found by Heiss *et al.*[1]. Our experience[2] was quite different and the reasons can be summarized as follows. (1) To stimulate an efficacious erythropoietic response r-HuEPO should be combined with adequate iron supplementation. This is difficult to achieve by oral iron therapy alone[3] as in the protocols of Kettelhack *et al.* and Heiss *et al.* In our trial[2] iron was given intravenously and, despite a lower total dose of r-HuEPO (600 U/kg), a significant increase in preoperative haemoglobin level and a reduction of homologous blood transfusions were obtained. (2) Preoperative r-HuEPO therapy for 15 days was necessary to obtain stimulation of erythropoiesis. A shorter period (5 days by Kettelhack *et al.* and 10 days by Heiss *et al.*) is not sufficient. Heiss *et al.* reported that the short period of preoperative treatment and the inadequacy of oral iron supplementation were probable causes of failure of treatment[1].

We recently demonstrated[4] that a significant increase of haemoglobin level can also be obtained by increasing intravenous iron dose (125 mg daily for 14 days) and reducing the dose of r-HuEPO (four doses of 100 U/kg every 4 days). This also allowed a reduction in the costs of therapy.

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1 Heiss MM, Tarabichi A, Delanoff C *et al.* Perisurgical erythropoietin application in anaemic patients with colorectal cancer: a double blind randomized study. *Surgery* 1996; **119**: 523–7.
2 Braga M, Gianotti L, Vignali A *et al.* Evaluation of recombinant human erythropoietin to facilitate autologous blood donation before surgery in anaemic patients with cancer of the gastrointestinal tract. *Br J Surg* 1995; **82**: 1637–40.
3 Mercuriali F, Zanella A, Barosi G *et al.* Use of erythropoietin to increase the volume of autologous blood donated by orthopaedic patients. *Transfusion* 1993; **33**: 55–60.
4 Braga M, Gianotti L, Gentilini O *et al.* Erythropoiesis after therapy with recombinant human erythropoietin: a dose-response study in anaemic cancer surgical patients. *Vox Sanguinis* (in press).

Outcome following laparoscopic resection for colorectal cancer

Sir

Psaila *et al.* report that this approach (*Br J Surg* 1998; 85: 662–4) involves early benefits for patients. We agree that laparoscopic procedures should be reserved for patients with simpler problems.[1] However, we think that the present study does not allow the authors to state that the laparoscopic approach has significant benefits. One of the major biases in the study is patient selection.

The authors reserved the open approach for the most difficult cases (gross obesity or large tumours). When surgery (laparoscopic or open) is performed for such patients, hospital stay is longer, morphine requirement is higher and postoperative morbidity is higher. The authors reported that there was a similar level of anastomosis (median 3 cm above the anal verge) for the two groups after anterior resection. The patients undergoing laparoscopic resection had tumours situated mostly in the upper third of the rectum (median 13 *versus* 7 cm). Was the authors' policy to perform a routine total mesorectal excision?

Even though one randomized trial suggested that laparoscopic colectomy for cancer improves the short-term outcome[2] two others concluded that the differences were unproved[3,4]. The sample sizes of these trials were too small to allow relevant conclusions.

At present, the feasibility of laparoscopic colorectal resection is clearly proved. The results from large trials in Europe and the USA will eventually lead to an evidence-based decision on which procedure is best.

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1 Slim K, Pezet D, Riff Y, Clark E, Chipponi J. High morbidity rate after converted laparoscopic colorectal surgery. *Br J Surg* 1995; **82**: 1406–8.
2 Lacy AM, Garcia-Valdecasas JC, Piqué JM *et al.* Short-term outcome analysis of a randomized study comparing laparoscopic *versus* open colectomy for cancer. *Surg Endosc* 1995; 9: 1101–5.
3 Stage JG, Schulze S, Møller P *et al.* Prospective randomized study of laparoscopic *versus* open colonic resection for adenocarcinoma. *Br J Surg* 1997; **84**: 391–6.
4 Ortiz H, Armendariz P, Yarnoz C. Early postoperative feeding after elective colorectal surgery is not a benefit unique to laparoscopy-assisted procedures. *Int J Colorect Dis* 1996; **11**: 246–9.

British Journal of Surgery 1998, 85, 1308–1309

Book reviews

Postgraduate Surgery: The Candidate's Guide. 2nd ed.

M. A. R. Al-Fallouji (ed). 275 × 205 mm. Pp. 665. Illustrated. 1998. Oxford: Butterworth-Heinemann. £75.

This is a mini-reference book in surgery, a revision guide aimed primarily at those sitting the MRCS/AFRCS examinations of the Royal Colleges. It outlines the developments and recent changes in surgical training and provides details of the new syllabuses, including those associated with higher surgical training. This second edition has been revised and updated to include new advances in surgery. The sections on pathophysiology, intensive care and preoperative patient selection are well researched. Other sections, however, are more basic but this volume does not aim to be fully comprehensive. It is easy to read and fulfils the author's aims of orientating the candidate towards selective topics, common clinical cases and surgical procedures. The gap in the market in this area has recently narrowed as a result of the more structured nature of both the examinations and preparation modules issued by the Colleges. However, the book serves as a useful practical guide designed primarily to help the candidate achieve success.

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Textbook of Surgery. 2nd ed.

I. Ahsan. 279 × 214 mm. Pp. 432. Illustrated. 1997. Amsterdam: Harwood Academic Publishers. £49.

This is the second edition of a textbook of surgery aimed at undergraduates, nurses and junior doctors. It has a uniquely Eastern flavour, in both the text and illustrations. This is well illustrated in the photographs of advanced pathology not normally seen in Western practices. However, the addition of a colour photographic quiz at the end of the book is redundant and these illustrations could have been incorporated within the text; this type of quiz rarely reproduces well and can be very difficult to interpret in isolation. It is possible that production considerations affected the layout of the book in this regard but this did not contribute positively to the volume. The practical sections, for example that on intravenous fluids, are full of easily assimilated and sound advice. The same is true of many of the conditions with which the author appears familiar and comfortable; however, I disagree with some of his recommendations elsewhere. The only treatment recommended in the management of diverticulitis is a preliminary colostomy in those who require emergency surgery. The book is competing in a very crowded market which makes it unlikely that it will be adopted as a standard text in Western universities where parochial interests lead to recommendations of more locally based texts. There is no reason why such constraints should not apply equally where this author teaches. The textbook will be valuable in the Indian subcontinent and throughout the developing world. As an introductory text to surgery in general it would serve equally well in the Western world.

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New Perspectives in Prostate Cancer

A. Belldegrun, R. S. Kirby and T. Oliver (eds). 282 × 192 mm. Pp. 429. Illustrated. 1998. Oxford: Isis Medical Media. £95.

This book summarizes highlights of the Second International Forum on Prostate Cancer held in London at the end of 1996. It is amazing how quickly the field moves on. It is one of a number of current textbooks on prostate disease reflecting greater interest and greater awareness, but is a very mixed volume with some quite detailed chapters while others are very superficial. The field is, however, fairly well covered overall and there are some innovative chapters, such as those on prostate cancer and diet, prostate cancer in the Middle East, and charitable support. It is not really clear which audience the text is supposed to address. It was interesting to read a patient's perspective on a radical prostatectomy, although one wonders how representative this man's experience was. I was also surprised that, when asked to counsel others about his experience, this patient explains 'how little time his surgeon will be able to spend with him once the operation is over'.

While it is good to see a mix of European and North American writers, both scientists and clinicians, this book offers much the same as its competitors and fails to deliver new insights to help with the diagnosis and management of prostate cancer. It could be useful for non-specialists and trainees to skim through to give some basic insight into some aspects of prostate cancer as it was understood 18 months ago.

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Detection and Treatment of Breast Cancer. 2nd ed.

I. S. Fentiman. 252 × 192 mm. Pp. 344. Illustrated. 1998. London: Martin Dunitz. £59.95.

When this volume appeared on my desk, I thought it was yet another textbook about breast cancer. I had a copy of the first edition, which I had dipped into from time to time, and I expected this book to be an update of that version. I was wrong. This second edition is not like a standard textbook. It attempts to bring together all the evidence about the diagnosis and treatment of breast cancer. It is not full of pretty photographs, but has many tables which are meta-analyses of the subjects being discussed. For instance, in Chapter 15, the question of hormone replacement therapy (HRT) and breast cancer is discussed. Table 15:13 is a meta-analysis of the relative risks of breast cancer in women taking HRT and it brings together all the published results available at the present time. The chapter goes on to discuss the risks of dying from breast cancer in women who have previously taken HRT and discusses HRT use after the treatment of breast cancer. Although this information will be useful to surgeons who advise women with breast cancer about HRT, it will be out of date very soon and, perhaps, this is the drawback of this book. I wonder if the publishers, and Professor Fentiman, have considered putting a version on the Internet? I think that this book should be available to all units who train breast surgeons; it will be valuable to all who treat breast cancer. It has some excellent quotations at the head of each chapter.

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Mastery of Cardiothoracic Surgery

L. R. Kaiser, I. L. Kron and T. L. Spray (eds).
284 × 218 mm. Pp. 976. Illustrated. 1997. Philadelphia, Pennsylvania: Lippincott-Raven. $201.25.

Mastery of Cardiothoracic Surgery is a first edition in this specialty, stemming from the original *Mastery of Surgery* published in 1984. The three editors have assembled a group of 132 distinguished authors contributing to the 92 chapters covering the whole range of cardiothoracic surgery. Like its ancestor it is a practical textbook, filling the gap between the well established theoretical text and atlases of cardiothoracic surgery. Each chapter is written by an author who is a well recognized expert in that particular field. The surgeon concentrates on his own practical approach to the problem, sharing his surgical philosophy with the reader. The text is supplemented by beautiful illustrations of the key points of operative procedures. There is a short bibliography at the end of each chapter. Finally, this book is unique in allowing the three principal editors to comment on the approaches offered by the individual chapter authors. The work is very comprehensive but, in a rapidly changing field, the current topics of minimally invasive cardiac surgery and transmyocardial laser revascularization receive little attention. This is inevitable given the current pace of change within the specialty at present. *Mastery of Cardiothoracic Surgery* is written by masters in their field. Its lessons are of value to both surgeons in training and established cardiothoracic surgeons. It should be present in every departmental library and will make a proud addition to my own personal library.

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Advances in Head and Neck Oncology

K. T. Robbins (ed.). 260 × 180 mm. Pp. 181. Illustrated. 1998. San Diego, California: Singular Publishing Group. £67.50.

The multiple authors in this short book provide the reader with a series of updates covering a wide range of topics relevant to the current practice of head and neck oncology. The extensively referenced chapters give the impression of being on solid ground rather than at the cutting edge. The opening chapter covers tumour biology, oncogenes and apoptosis. This firmly establishes the science behind current treatments. The developments in radiation therapy fractionation are discussed with reference to recently completed trials in Europe and the USA. Intra-arterial chemotherapy is not new but the author presents promising results using targeted cisplatin therapy for patients with advanced malignant disease. Primary endoscopic surgery for early laryngeal cancer and near total laryngectomy for advanced primary tumours represent the extremes of surgical practice. These procedures are not commonplace in the UK where radiotherapy holds sway for T_1 to T_3 tumours. Perhaps we need to look beyond total laryngectomy as one operation to fit all. Neck dissection has moved a long way from Crile's original description; selective neck dissection is discussed for the treatment of N0 and N+ cases. Developments in surgical technique often parallel technological advances. The two chapters covering surgical routes to the nasopharynx and the reconstruction of the mandibular arch highlight both the ingenuity and complexity of surgery in this region. They illustrate the need for multidisciplinary co-operation in the treatment of these cases. The past 15 years have seen real advances in functional outcome following treatment for upper aerodigestive tract tumours. These are discussed with particular reference to voice rehabilitation following laryngectomy. The concepts of quality of life measurement, comorbidity and cost effectiveness of treatment occupy the final chapter and indicate the need to be patient-focused at all times. Overall, this book provides an insight into some of the advances and innovations made during the past decade in head and neck surgery. It is not comprehensive but it is well written and sufficiently broad in content to attract the non-surgeon reader. It should find shelf space in the otolaryngologist head and neck surgeon's library.

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An Introduction to Vascular Biology. From Physiology to Pathophysiology

A. Halliday, H. Blunt, L. Poston and M. Schachter (eds).
228 × 151 mm. Pp. 273. Illustrated. 1998. Cambridge: Cambridge University Press. £24.95.

This is an excellent little book, which is designed to introduce vascular biology to the uninitiated. As the authors themselves note, each year produces vast amounts of new knowledge on the subject and a book like this can quickly fall out of date. However, allowing for this, it makes excellent reading. The chapters are written by separate authors and there is inevitably some degree of overlap. However, for readers who are interested in gaining a fundamental understanding of this critical area, I believe the book offers an excellent pathway towards this goal. Chapters are, in general, succinct, which allows one to read the book in stages. There is an excellent section on the endothelial cell and an easy-to-read chapter on mechanisms of atherosclerosis. However, the book is not complete. There is, for example, a surprising absence of a section on haemorheology and thrombosis. In addition, there is no specific section on venous pathophysiology. Some might consider these areas to be more relevant to vascular biology than, for example, wound healing, which has a chapter of its own. This volume is not for the faint-hearted. None the less, for those who are interested in having anything more than a vague understanding of vascular biology, it provides an excellent reference manual and gives the reader some idea of the enormous amount of work that has been carried out in this area. In addition, it provides the vascular surgeon with a well referenced and readable collection of papers on what is becoming a fundamental part of our understanding of atherosclerosis.

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Scientific Surgery

The British Journal of Surgery is committed to practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English language publications. The full list of all these papers will be available in the Scientific Surgery Archive which will be held on *The British Journal of Surgery* website together with links to free Medline sites where abstracts can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Randomized trials

Barth Jr RJ, Burchard KW, Tosteson A, Sutton Jr JE, Colacchio TA, Henriques HF *et al.* Short term outcome after mesh or Shouldice herniorrhaphy: a randomized prospective study.
Surgery 1998; 123: 121–6.
No differences in pain scores or time to return to work in the 105 patients studied.

Hall JC, Christiansen KJ, Goodman M, Lawrence-Brown M, Prendergast FJ, Rosenberg P *et al.* Duration of antimicrobial prophylaxis in vascular surgery.
Am J Surg 1998; 175: 87–90.
In this study of 302 patients, multiple doses of antibiotics given until all invasive lines were removed reduced the risk of wound infection to 10 per cent from 18 per cent in patients who had only a single dose.

Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R *et al.* A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation.
N Engl J Med 1998; 338: 791–7.
Significant bleeding was reduced from 3·8 per cent with sucralfate to 1·7 per cent by ranitidine (50 mg intravenously every 8 h) in a study of 1200 patients

Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs.
N Engl J Med 1998; 338: 1105–11.
Urokinase reduced the need for surgery but did not influence outcome in the 548 patients randomized: amputation free survival at 6 months was 71·8 *versus* 74·8 per cent after initial surgery.

Tetteroo E, van der Graaf Y, Bosch JL, van Engelen AD, Hunink MGM, Eikelboom BC *et al.* Randomised comparison of primary stent placement *versus* primary angioplasty followed by selective stent placement in patients with iliac artery occlusive disease.
Lancet 1998; 9110: 1153–9.
This multicentre study of 279 patients documented no difference in outcome between the two methods; only 43 per cent of patients in the selective group required stent placement which was cheaper and therefore preferable.

Randolph A, Cook DJ, Gonzales CA, Andrew M. Benefit of heparin in peripheral venous and arterial catheters: a systematic review and meta-analysis of randomised controlled trials.
BMJ 1998; 316: 969–75.
Heparin flushing had no advantage over saline in this review of 26 randomized trials.

Kubota K, Makuuchi M, Noie T, Kusaka K, Sakamoto Y, Miki K *et al.* Risk factors for hyperamylasemia after hepatectomy using the Pringle maneuver: randomized analysis of surgical parameters.
Arch Surg 1998; 133: 303–8.
The Pringle manoeuvre did not appear to affect amylase production in a study of 40 patients.

Merad F, Yahchouchi E, Hay J-M, Fingerhut A, Laborde Y, Langlois-Zantain O. Prophylactic abdominal drainage after elective colonic resection and suprapromontary anastomosis: a multicenter study controlled by randomization.
Arch Surg 1998; 133: 309–15.
In this study of 319 patients, drainage did not reduce the risk of complications such as anastomotic leakage – 9 *versus* 8 per cent with no drain.

Abraham E, Anzueto A, Gutierrez G, Tessler S, San Pedro G, Wunderink R *et al.* Double blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock.
Lancet 1998; 9107: 929–33.
Mortality and adverse event rates were not affected in this trial including 1878 patients: 40·3 per cent treated patients died within 28 days *versus* 42·8 per cent controls.

Klingler A, Henle KP, Beller S, Rechner J, Zerz A, Wetscher GJ *et al.* Laparoscopic appendectomy does not change the incidence of postoperative infectious complications.
Am J Surg 1998; 175: 232–5.
Some 169 patients were randomized, 75 per cent had appendicitis. Postoperative stay was reduced from 4 to 3 days after laparoscopic appendicectomy, but wound infection rates were similar – 6 *versus* 7 per cent open.

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British Journal of Surgery 1998, 85, 1313–1315

Leading articles

Pancreas and islet transplantation

A leading article on the subject of pancreas and islet transplantation as a treatment for diabetes, published in this journal 6 years ago[1], drew a number of conclusions which may now be usefully re-examined. In 1992 there was no conclusive evidence that the restoration of normoglycaemia would prevent the complications of diabetes and the effect of vascularized pancreas transplantation on such complications was not fully established. Pancreas transplantation seemed likely to remain restricted to a small subset of the diabetic population and human islet transplantation was in its infancy, with many problems still to be resolved. Finally, it was suggested that the safety and efficacy of human islet transplantation would be investigated over the next few years.

We now have an answer to the question of whether the restoration of normoglycaemia will prevent the complications of diabetes. The Diabetes Control and Complications Trial[2], in which patients were randomized to conventional twice daily subcutaneous insulin injections or to more intensive therapy, has convincingly shown that improved glycaemic control is associated with a decrease in both the incidence and progression of the microvascular complications of diabetes. The findings of this trial have been widely accepted and in 1998 this concept is no longer controversial.

The number of vascularized pancreas transplants performed has continued to increase and over 9000 cases have now been reported to the International Pancreas Transplant Registry[3]. The majority are simultaneous pancreas and kidney transplants, although an increasing number of pancreas transplants alone are now being carried out. For simultaneous pancreas plus kidney transplants, the results continue to improve, with 1-year graft and patient survival rates of 89 and 94 per cent respectively. It has been shown convincingly that the quality of life of patients who receive a simultaneous pancreas plus kidney transplant, rather than a kidney transplant alone, is improved; there is also some improvement in peripheral neuropathy and stabilization of retinopathy. There is no conclusive evidence so far that pancreas transplantation reduces the progression of diabetic complications.

Of concern is the growing awareness that simultaneous pancreas and kidney transplantation may carry a considerable associated morbidity and even an excess mortality rate compared with kidney transplantation alone[4]. Furthermore, simultaneous transplantation seems to be associated with more episodes of infection, rejection, hospital admission and surgical complications than a single-organ kidney transplant. The issue of who should receive a combined transplant rather than a kidney alone also remains controversial. A reasonable viewpoint[5] is that patients with stable diabetes receiving a renal transplant should be offered a pancreas simultaneously, with the proviso they are made aware of and understand the increased associated morbidity and mortality rate associated with the combined procedure.

One of the most contentious areas in the field of vascularized pancreas transplantation is whether non-uraemic diabetic patients should receive a vascularized pancreas transplant. It has been suggested that the non-uraemic diabetic patient with serious problems, such as hypoglycaemic unawareness or brittle diabetes, should be offered a pancreas transplant in the expectation that the risks of immunosuppression and the complications of surgery are preferable to uncontrolled diabetes. The Minneapolis group have recently reported their experience of 225 single-organ pancreas transplants[6]. If tacrolimus was used as the immunosuppressive agent, at 1 year graft survival was 80 per cent and patient survival was 90 per cent. Successful transplantation in this group of patients improves quality of life, but at a price of the immediate risk of surgery, the risk of immunosuppression and a 3 per cent risk of immunosuppression-related lymphoma.

Whereas vascularized pancreas transplantation has generally been offered to diabetics with established complications, islet transplantation might theoretically be offered to newly diagnosed diabetic patients in an attempt to prevent such complications. The reasons are, first, that islet transplantation is a relatively minor surgical procedure and, second, that it might be possible to immunomodulate islets before transplantation, obviating the need for lifelong immunosuppression. It was reported in the 1970s that islet transplantation could cure diabetes in rats and mice, and at that time it was widely predicted that successful human islet transplantation was only a few years away. Sadly, although there have been significant advances in techniques for the isolation of human islets, this form of transplantation has proved much more challenging than the early animal experiments suggested.

There are now over 300 reports of islet allotransplantation[7], generally in type I diabetic patients. Most of these transplants have been performed at the same time as a kidney transplant. Although patient survival at 1 year is 93 per cent, only 14 per cent of patients are insulin independent at that time. The reasons for the failure of islet allotransplantation are numerous[8,9], but foremost are difficulty in isolating large numbers of islets due to the vagaries of the required collagenase digestion process, difficulty in detecting rejection, and metabolic dysfunction of islets after transplantation into ectopic sites such as the liver. Finally, although it has proven relatively straightforward to immunomodulate rodent islets, this has been difficult to achieve in large animals; to date there are no examples of successful immunomodulation of human islets.

Alternative strategies in human islet transplantation, such as immunoprotection in microcapsules, have been thwarted by foreign body reaction to the capsular material. In addition, the prospect of porcine islet xenotransplantation into humans has been damaged by recent reports of retrovirus transmission from porcine to human cells in tissue culture[10]. Despite an immense amount of research and effort, there has been a frustrating lack of progress in human islet transplantation over the past 6 years.

What then is the current state of pancreas and islet transplantation compared with the situation in 1992? With respect to vascularized pancreas transplantation, although its safety and efficacy have improved, it is still only applicable to a small fraction of the diabetic population. The effect of vascularized pancreas transplantation on diabetic complications has yet to be fully established. The crucial issue is whether the benefit of a combined transplant compared with a single-organ kidney transplant alone is worth the risk. While the safety of human islet transplantation seems proven, its efficacy is not. The statement in 1992, that such transplantation is in its infancy with many problems still to be resolved, remains true in 1998.

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Registers for patients with familial tumours: from controversial areas to common guidelines

Periodic clinical screening of individuals with a predisposition for an inherited tumour syndrome improves both prognosis and life expectancy. Potentially life-threatening tumours can be removed in the premalignant stage of inevitable tumour progression.

The responsibility for continuity in periodic clinical screening may place a heavy burden on the attending physician. Periodic control cannot be guaranteed if there is departure of the lead physician, loss of funds or facilities, conclusion of short-term research programmes or movement of patients. Such factors interrupt the continuity and can be disturbing to the families; frustration arises and people feel neglected. One way to solve such practical problems has been to organize the administrative work centrally and to leave the physician to perform clinical screening work. This provides the advantages of central registration, promotion of early detection and improved clinical management. Disadvantages may include psychological burden and violation of privacy. Case identification and follow-up should be a continuing process and not a short-term project[1].

In 1981, a pilot study was initiated in the Netherlands to explore the feasibility of a nationally coordinated register combined with decentralized clinical screening of large groups of family members. Registration was on a voluntary basis by both family members and physicians. Assistance of centrally appointed nurse geneticists who visited the families at home was helpful in collecting blood samples and constructing pedigrees. A similar experience was obtained in the UK[2]. After 3 years, large groups of patients and their relatives were being handled effectively and regulations were compiled to protect civil rights concerning privacy. Written permission and informed consent were necessary for registration of data. Patients and relatives had the right to refuse registration, to have sight of their own data and to have their medical data destroyed. Personal and medical data were stored separately, and no information on registered subjects was supplied to a third party without consent. Medieal data might be used for scientific publications only with the consent of the physician concerned.

A coordinate registration facility serves more functions than registration, supervision of privacy and maintenance of screening[3]. Identification of families at risk involves the responsibility to make available general facilities, such as guidelines for diagnosis, treatment and attendance. Families become less dependent on one physician and accept some responsibilities if information is provided (distribution of information booklets for families and general practitioners, assistance to family support groups) to allow them to become fully involved in discussions and decision making.

Hereditary cancer syndromes represent an area of rapid development in basic science and clinical medicine, but time is required to come to agreement about topics such as DNA diagnosis and new forms of clinical management. To avoid confusion in families, explicit and common guidelines are needed for patient identification, treatment and follow-up. Attention has to be paid to the age at which DNA analysis should be performed, the procedures of disclosure of DNA test results, counselling of families by the attending specialist, arrangement of psychological attendance, and follow-up after diagnosis[4]. Consensus must be obtained about medical and surgical treatment (conservative follow-up *versus* aggressive treatment).

For specific families with distinct mutations, genotype–phenotype correlation studies help to assess strategies for management. Methods of assessing genotype–phenotype correlation include the study of large families, periodic screening of all affected family members and the use of extensive screening procedures. Because hereditary tumours are uncommon, patients are better served if strategies are based on the results of collaborative multicentre studies. Such studies may be organized by the coordination centre in order to collect extensive data about follow-up and to resolve controversial areas in clinical management.

The centre has to develop a generally accepted point of view on strategy of approach and analysis of patients with apparently sporadic tumours. Specific information about the risk of having a hereditary disease may depend on family history, multicentricity of tumour localization and a young age of occurrence. Assessment or exclusion of the diagnosis of hereditary disease means that the privacy of the family is involved. The attending physician must realize that there is an obligation in accepting these consequences. Initially, information about the disease has to be provided to the patient, as well as information on the consequences of being a carrier of an inherited disease. If a decision to start family investigation is made, continuity must be maintained.

Open communication is needed among medical professionals, families and volunteer organizations such as family support groups. In the Netherlands, experience has shown that appropriate information can prevent psychological problems: 'One suffers most by anxiety about suffering' (i.e. painful or apprehensive uneasiness of mind over an impending illness). Signs may exist such as sweating, tension and increased pulse rate. To avoid this, adequate information must be provided and this has been a main reason for the development of family support groups.

Family support groups provide individual patients and their relatives with information, emotional support (companionship in distress), and material or instrumental support (discussion of common interests with respect to ethical, legal and social aspects, such as employment and insurance)[5,6]. A family support group is perhaps not the ideal solution because privacy is involved and a threshold is felt by candidate members. On the other hand, receiving information allows members to recognize their problems as common issues. During the past two decades a radical change in attitude has been observed. In the past, the occurrence of disease in a family was a closely guarded family secret; the fear of humiliating disgrace or disrepute was a burden to the family. To admit a familial predisposition to a disease meant dishonour, shame and disgrace. If acknowledged in the neighbourhood, isolation of the family could be the result, with lost opportunities of children for marriage and future insurance, and for employment. Currently, nearly all taboos have been broken down, the authority of physicians has vanished and there is openness in communication about familial disease. The taboo of the past has been replaced by open discussion of issues. There is less feeling of shame or guilt. The pressure of predestination in the past has been replaced by knowledge about predisposition and the consequences for the future; the original sin has become a DNA (genetic) defect. In the Netherlands, family support groups for multiple endocrine neoplasia, von Hippel–Lindau disease and colonic cancer have made these diseases an issue that can be discussed in a way that allows resolution of many specific problems.

In conclusion, a coordinated register of families with hereditary tumours may serve common, practical issues. It maintains an inventory and promotes early detection and clinical management of disease gene carriers. It allows the distribution of information booklets for families and general practitioners. It supports a centralized facility for DNA analysis. It underpins the organization of common guideline meetings and is of significance to family support groups. If properly organized and managed, such a central register may greatly benefit the well-being of patients and their family members.

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British Journal of Surgery 1998, 85, 1319–1331

Review

Hepatocellular carcinoma

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Background Hepatocellular carcinoma is one of the world's most common malignancies. The aims of the present paper are to review data on (1) epidemiology and screening programmes for the early detection of the tumour and (2) advances in the diagnostic imaging and management.

Methods Relevant English language articles, published between January 1985 and December 1997, were reviewed. Articles were identified through Medline search, using the key words 'hepatocellular carcinoma'. Articles cited in the bibliographies of these articles were searched manually.

Results Hepatocellular carcinoma has a heterogeneous geographical distribution. Although its risk factors have been identified, the efficacy of screening programmes remains uncertain. Imaging has improved substantially with the recent application of dual-phase helical computed tomography and magnetic resonance imaging employing specific contrast agents. The comparative efficacy of conservative therapy and surgical resection is uncertain, since well controlled trials are lacking.

Conclusion Hepatocellular carcinoma is commonly a problem of two diseases, the malignancy itself and cirrhosis. This renders treatment rarely curative, even when surgical resection can be applied in a technically successful sense. Liver transplantation could be a definitive treatment but this is plagued by limited donor resources.

Hepatocellular carcinoma (HCC) is one of the world's most common malignancies[1], causing almost one million deaths annually. HCC has a heterogeneous geographical distribution, which is probably related to differences in prevalence of risk factors among separate world areas[1–3]. It is one of the most frequently occurring neoplasms in Asia, Africa and the Mediterranean basin. In the USA approximately 6000 new cases are diagnosed each year[4]. HCC usually develops on a background of chronic inflammatory liver disease and in most cases is a problem of two diseases, the malignancy itself and cirrhosis; the latter is usually a result of chronic hepatitis. While the aetiology of chronic hepatitis may vary, the morphological processes and the end result are quite similar: necrosis, fibrosis, regeneration and, frequently, the emergence of portal hypertension and/or liver failure[5–8]. Like variceal bleeding, encephalopathy and ascites, HCC is a potential complication of cirrhosis[9].

During the past few years intensive research has provided important new information regarding the epidemiology of HCC, and has led to considerable progress in our ability to diagnose and potentially treat this tumour at an early stage. A major advance was the application of multimodality treatment protocols in specialized units employing the coordinated skills of experienced hepatologists, invasive radiologists and hepatobiliary surgeons. This paper reviews the latest data on the epidemiology of HCC, screening programmes for patients at risk of the disease, the recent developments which facilitate diagnosis at an early stage and advances in management.

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Epidemiology

Incidence and prevalence

HCC has a high incidence in sub-Saharan Africa, mainly Mozambique and Zimbabwe, and south-east China and Taiwan, which exceeds 30 cases per 100 000 per year (*Table 1*). Among developed countries, Japan has the highest incidence, reaching 15 cases per 100 000 per year, while the remaining developed countries have an intermediate (southern Europe five to ten cases per 100 000 per year) or low (northern Europe and USA less than five cases per 100 000 per year) incidence[1–3]. In the past decade, the incidence rates for HCC seem to have changed in several countries, and it is debated whether this phenomenon is due to an improved efficacy of diagnostic tools or a real increase as a consequence of changes in risk factors. Data from Japan suggest that the rising incidence may be due to an increase in the

Table 1 Annual incidence of hepatocellular carcinoma per 100 000 population

Country	Men	Women
High-risk areas		
Mozambique, Zimbabwe, China, Taiwan	30–120	9–30
Japan, South Africa, Greece	10–30	3–9
Intermediate-risk areas		
Southern Europe (Spain, Italy, France), Switzerland, Argentina	5–10	2–5
Low-risk areas		
Northern Europe, USA, Canada, India	<5	<3

prevalence of hepatitis C virus (HCV) infection in the general population[5,10].

Risk factors

Several epidemiological studies provide evidence that the main risk factors for HCC are age, sex and cirrhosis of any aetiology, but that HCC is mainly due to alcohol abuse and/or chronic infection with hepatitis B virus (HBV) or HCV. The relative roles of HBV and HCV infection in hepatocellular carcinogenesis vary considerably among populations[11] (*Table 2*). A synergistic effect on risk for HCC has recently been reported when both HBV and HCV markers are present[11].

Age and sex. The relationship with age probably reflects the time lag between acquisition of the risk factors (HCV or HBV) and the development of cancer. It is noteworthy that in some endemic HBV areas with a higher incidence of vertical transmission of HBV, such as Mozambique or the coastal areas of mainland China, HCC develops in young people. Regarding sex, all over the world there is a male preponderance, the male:female ratio being around 4:1[12].

Cirrhosis. Cirrhosis is the most important risk factor associated with HCC[6,8,13,14]. In Spain, cirrhosis underlies HCC in more than 80 per cent of cases[15]. The annual incidence of HCC among patients with cirrhosis ranges from 3 to 5 per cent[6,16,17]. Data obtained in Barcelona have shown that 5 per cent of compensated cirrhotics are diagnosed with HCC if investigated intentionally; this percentage rises to 15 per cent when studying patients with cirrhosis bleeding from gastro-oesophageal varices or to 20 per cent when they develop spontaneous bacterial peritonitis[18–20]. On the other hand, some autopsy studies of patients with cirrhosis carried out in Japan, Italy and the USA have shown a prevalence of HCC ranging from 20 to 80 per cent[5,10].

Hepatitis B virus. HBV is an important factor in the development of HCC[5]. The association between HBV and HCC was suggested by the high incidence rates of HCC in regions where HBV infection is hyperendemic. In addition, follow-up studies have shown that HBV carriers have a significant risk of HCC which is particularly high in subjects with chronic liver disease, while in healthy carriers without chronic liver damage the risk is not considered to be as high[8,21]. The oncogenic mechanism of HBV is thought to be based on the genetic damage associated with chronic inflammation and with the integration of HBV DNA into the host genome[5,22].

Hepatitis C virus. Epidemiological studies have shown that HCV is likely to be associated with the occurrence of HCC[23,24]. The prevalence of anti-HCV antibodies among patients with HCC ranges from 70 to 80 per cent in southern Europe and Japan, to around 30 per cent in China and South Africa. Chronic HCV infection co-exists with HBV infection or alcohol abuse in about 20 per cent of cases, possibly interacting in the development of HCC[11,23]. Although patients with chronic HCV infection have an increased risk of developing HCC, there is no evidence for a direct oncogenic role for this agent, and it is thought that HCV may promote HCC through induction of chronic necroinflammatory hepatic activity and liver cirrhosis. HCC has seldom been documented in a normal HCV-positive liver, while most cases develop in the setting of HCV-related cirrhosis[25].

Alcohol. Although ethanol is not in itself a carcinogen, a number of laboratory and epidemiological studies attribute an indirect role to ethanol in hepatocarcinogenesis. Some authors have suggested that alcohol and HCV infection may act synergistically, since patients with alcoholic cirrhosis associated with HCV infection have a higher prevalence of HCC than those with either factor alone[14,26].

Aflatoxins. These potent carcinogenic agents may contaminate food stores in humid conditions, and epidemiological surveys have shown a correlation between the degree of contamination and incidence of HCC[27,28]. A recent study from Taiwan has demonstrated a multivariate-adjusted odds ratio of developing HCC of 5·5 for patients with detectable serum levels of aflatoxin B1[27]. Aflatoxin B1 induces a mutation at codon 249 of *p53*[5] and this may be one of the mechanisms leading to the development of HCC. However, there is an overlap of the areas with high aflatoxin contamination and areas with a high HBV infection rate and so the oncogenic action of aflatoxin may be in part the effect of its synergism with HBV.

Oral contraceptives. In most of the case–control studies performed to determine whether sex hormone contraceptives increase the risk of HCC in women, the influence of HBV/HCV infections and other potential confounders, such as alcohol consumption, has not been analysed. The relative risk estimate varies from twofold to fourfold for women who are oral contraceptive users in non-endemic hepatitis regions to only onefold in women from endemic hepatitis areas. Because of the existing uncertainties, a large case–control study has been performed in six European countries[29] and the results will probably clarify whether oral contraceptives increase the risk of developing HCC.

Table 2 Prevalence of risk factors in patients with hepatocellular carcinoma: geographical differences

	Prevalence (%)				
	Southern Europe (Spain, Italy, France)	Japan	USA	South Africa	China and Taiwan
Cirrhosis	90	80	70	60	80
Anti HCV antibodies*	60–80	70	30–60	30	30
HBsAg	5–10	20	15	50	60–90
Alcohol	15–30	<10		<10	<10

*Including association with hepatitis B surface antigen (HBsAg) or alcohol. HCV, hepatitis C

Screening programmes

Potential curative treatments can only be applied at an early stage of HCC which in most cases develops in the setting of cirrhosis[30]. Therefore screening programmes for HCC in patients with cirrhosis have been recommended by several authors[6,16,17,31,32] (*Table 3*); the usefulness of such a policy has not been established by prospective clinical trials. At present, despite the development of new diagnostic modalities which increase the frequency of detection of small tumours[33], there is no clear evidence that surveillance and early intervention leads to an increased cure rate[6,34]. Moreover, the cost effectiveness of such a plan in terms of years of life saved is not known.

The prognosis of HCC is generally grim because it is detected at an advanced stage. In the Barcelona Liver Unit, only around 20 per cent of patients with HCC can benefit from curative therapies, such as orthotopic liver transplantation (OLT), surgical resection and percutaneous ethanol injection (PEI). Although a lack of controlled trials precludes our knowing whether such treatment options improve survival, it is estimated by comparison with the outcome of historical cases that well selected patients may benefit from radical therapies, both in terms of antitumoral effect and survival. The 3-year survival rates after OLT, resection and PEI are around 75, 50–70 and 45–55 per cent respectively[30,35,36], while the corresponding figure for non-treated small HCC in patients with cirrhosis is only 25 per cent[37,38]. Therefore, any screening programme should address the early detection of asymptomatic tumours that can be treated with radical options, aiming at improving long-term prognosis.

Four conditions should be satisfied to recommend a screening programme for cancer. (1) The disease must be common, with a clear-cut population at risk. (2) There must be a non-invasive highly accurate diagnostic method. (3) There must be an established radical therapy. (4) The screening programme should be cost effective.

Population at risk

Screening programmes for early detection of HCC should be directed at a well selected population at risk. Screening can be divided into population-based and clinic-based programmes[39]. In the light of the epidemiological data presented above, in Western countries clinic-based programmes should be conducted in patients with cirrhosis, mainly those with chronic HBV or HCV infection or a history of alcohol abuse. Conversely, implementation of screening programmes in patients without cirrhosis would not lead to a potential benefit. Furthermore, when assessing programmes in terms of survival improvement or cost effectiveness (years of life saved), the early detection plans should be restricted to those who could be treated with radical curative therapies if diagnosed with HCC. Therefore, restrictive criteria of age, stage of liver disease and baseline conditions that would preclude radical therapy should be made clear when surveillance programmes are organized.

Screening tests

The most widely used screening tests for HCC are α-fetoprotein (AFP) determination and ultrasonography. The latter provides high sensitivity, specificity and predictive values, while AFP estimation lacks acceptable sensitivity in terms of early detection[6,16,17,40]. The interval between screening tests will affect both the proportion of HCCs detected and the cost of the programme. According to the data published on tumour growth rates, it seems reasonable that the interval between repeat scans should vary from 4 to 6 months. There may be a subgroup of patients with cirrhosis at particularly high risk of HCC. This group includes those with persistently raised serum AFP levels[6,41] (whose relative risk is 14 times higher than that of patients with normal AFP levels)[6] or with liver cirrhosis associated with morphological changes of liver cell dysplasia[42]. It is possible that these subgroups might benefit from special screening schedules or even that they might be the only ones in whom screening could be cost effective.

Applicability of radical treatments

There are no randomized controlled trials assessing the usefulness of screening programmes in the early detection of HCC and the potential benefit in patient survival. Nowadays, such a study would be almost impossible to perform ethically. Therefore, the only way to address this issue is to analyse carefully the outcome of cohorts of patients with cirrhosis submitted to regular follow-up[6,16,17,31,32]. However, the results of these studies are conflicting. In Asia, screening programmes have succeeded in both early recognition of HCC and increased applicability of potentially radical treatments, mainly surgical resection[31,43]. In Western countries, however, the available prospective studies have yielded controversial results. In a large screening study conducted in the West, Colombo *et al.*[6] did not find an increase in the rate of detection of potentially curable tumours, despite the fact that around 50 per cent of them were smaller than 5 cm. Three additional prospective surveillance programmes carried

Table 3 Screening programmes for detection of hepatocellular carcinoma in patients with cirrhosis

				Screening				
Reference	Year	No. of patients	No. with HCC	Modality	Interval (months)	Incidence (%)	HCC < 5 cm* (%)	Radical treatment(%)†
Oka *et al.*[31]	1990	140	40	US + AFP	3	6·5	33 (82)	15 (38)
Colombo *et al.*[6]	1991	447	56	US + AFP	12	3·2	30 (54)	12 (29)
Pateron *et al.*[16]	1994	118	14	US + AFP + DCP	6	5·8	6 (42)	2 (14)
Cottone *et al.*[17]	1994	147	30	US + AFP	6	4·4	25 (83)	10 (33)
Zoli *et al.*[32]	1996	164	34	US + AFP	3–6	6·2	26 (76)	7 (20)

*Single hepatocellular carcinoma (HCC) of less than 5 cm without vascular invasion or metastatic disease. †Surgical resection, orthotopic liver transplantation or percutaneous ethanol injection. US, ultrasonography; AFP, α-fetoprotein concentration; DCP, des-γ-carboxyprothrombin out in Western countries using ultrasonography and measurement of AFP concentrations at 6-month intervals have reported detection of single small HCCs in 42–83 per cent of cases[16,17,32]. However, these data were neither accompanied by a significant increase in applicability of radical therapies nor by an increase in survival rate. Further investigations should be designed to include only those patients who would be treated with potentially radical options if diagnosed with HCC and, in addition, patients diagnosed with HCC should be considered for OLT, resection or PEI if they fulfil the criteria for these options.

Cost effectiveness

Since there are no clinical trials, calculation of the cost of screening is based on theoretical models. It has been suggested recently that biannual screening using AFP and ultrasonography may provide substantial benefit (mean gain in life expectancy of 3–9 months) only in well targeted subgroups of patients (Child–Pugh stage A cirrhosis)[44]. The cost effectiveness of such strategies ranges from $26 000 to $55 000 for each additional life-year gained, even when surgical resection is considered as the only radical option. In the light of this, before recommending such expensive surveillance programmes, it is mandatory to develop solid therapeutic options with a clear-cut benefit in terms of survival.

Advances in the diagnostic imaging of hepatocellular carcinoma

Cirrhosis is characterized by the development of a spectrum of nodules, ranging from benign regenerating nodules to overtly malignant HCCs[45]. Therefore the ability to detect nodules that contain HCC at an early stage is critical for prompt resection or transplantation, possibly resulting in a significantly increased survival[46]. The term 'dysplastic nodule' – a nodular lesion of hepatocytes distinct from the surrounding liver parenchyma – has been adopted recently to replace confusing terms such as 'adenomatous hyperplastic nodule', 'macroregenerative nodule', 'ordinary adenomatous hyperplasia' etc., previously used to describe hepatocellular nodules in cirrhotic liver, which made an objective comparison of different studies difficult. Moreover, numerous terms, such as 'early HCC' and 'adenomatous hyperplasia with malignant foci' have also been used to describe dysplastic nodules that sometimes contain microscopic foci of HCC. A new terminology is currently in use for these nodules to clarify this issue[47]. A dysplastic nodule containing microscopic foci of HCC is called a 'dysplastic nodule with foci of HCC'. When a microscopic focus of HCC enlarges, but its diameter remains less than 2 cm, it is called 'small HCC'; when it is larger, it is called 'HCC'.

This new terminology emphasizes the concept that a regenerative nodule, a dysplastic nodule, a dysplastic nodule with microscopic foci of HCC, a small HCC and finally an obvious HCC represent a continuum in the development of HCC[48]. Imaging modalities such as dual-phase helical computed tomography (CT), thin-section magnetic resonance imaging (MRI), colour Doppler sonography, CT during arterial portography and CT after hepatic intra-arterial injection of iodized oil are promising *in vivo* tools to allow diagnosis of HCC at an early stage[49–53]. Sonography has a limited sensitivity for detecting HCC in patients with end-stage cirrhosis because of significant overlap in the sonographic appearance of benign nodules with small HCCs. CT arterial portography is also of limited value in the evaluation of patients with advanced cirrhosis because of diminished or even reversed portal blood flow. Finally, CT after injection of iodized oil through a catheter placed in the hepatic artery, although highly specific, has a limited sensitivity in the detection of small HCCs. Recent studies indicate that this technique does not seem to offer any clear advantage over state-of-the-art CT or MRI[54]. Therefore the following discussion is focused on these latter two modalities.

Dual-phase helical computed tomography

Dual-phase helical CT allows the hepatic arterial phase (HAP) and portal venous phase (PVP) of hepatic enhancement to be imaged separately. This is particularly useful for detecting hypervascular tumours rapidly becoming isoattenuating to liver. Since the liver receives 75–80 per cent of its blood flow from the portal vein, there is little enhancement of liver parenchyma during the HAP. Hypervascular tumours like HCC, however, which receive virtually all of their blood supply from the hepatic artery, receive contrast-enhanced blood without dilution during the HAP and appear as enhancing masses against the minimally enhanced liver parenchyma for about 20–30 s (*Fig. 1*). Imaging patients with HCC during the HAP will yield additional tumour detection (*Fig. 2*). Moreover, patients with HCC and concomitant cirrhosis, which usually results in increased hepatic arterial flow, will benefit more from imaging during the HAP[49].

Dysplastic nodules have mainly a portal venous supply and HCC a hepatic artery supply[55]. Therefore, it is conceivable that differentiation between a dysplastic nodule and an overt HCC might be made on the basis of differences in blood supply depicted by dual-phase CT. Problems arise in patients with chronic liver disease when one tries to detect a dysplastic nodule harbouring foci of HCC. A dysplastic nodule with foci of HCC (early HCC) is a small nodular lesion, usually less than 3 cm in size, without a fibrous capsule and with very small (microscopic) foci of HCC composed of well differentiated tumour cells with little architectural atypia. This lesion frequently contains portal structures and has a mainly portal blood supply. Consequently, it enhances like the rest of hepatic parenchyma (isoattenuation), which makes it impossible to be detected and differentiated. Recent reports indicate that CT during early and late liver enhancement has limited sensitivity (56 per cent), since approximately 45 per cent of these nodules are isoattenuating or unenhanced on HAP and PVP scans[56]. On the other hand, the development of an arterial blood supply in a dysplastic nodule signals its malignant transformation into an overtly malignant HCC (*Fig. 3*). Then dual-phase CT has a major role to play, depicting up to 95 per cent of tumour foci.

Magnetic resonance imaging

Until recently, reports have claimed unique *in vivo* magnetic resonance signal intensity characteristics for regenerative or dysplastic nodules, allowing them to be reliably differentiated from HCC. Hyperintensity on T2-weighted images (*Fig. 4*) is the feature distinguishing HCC from dysplastic nodules and regenerative nodules, demonstrating hypointensity or isointensity on T2-weighted

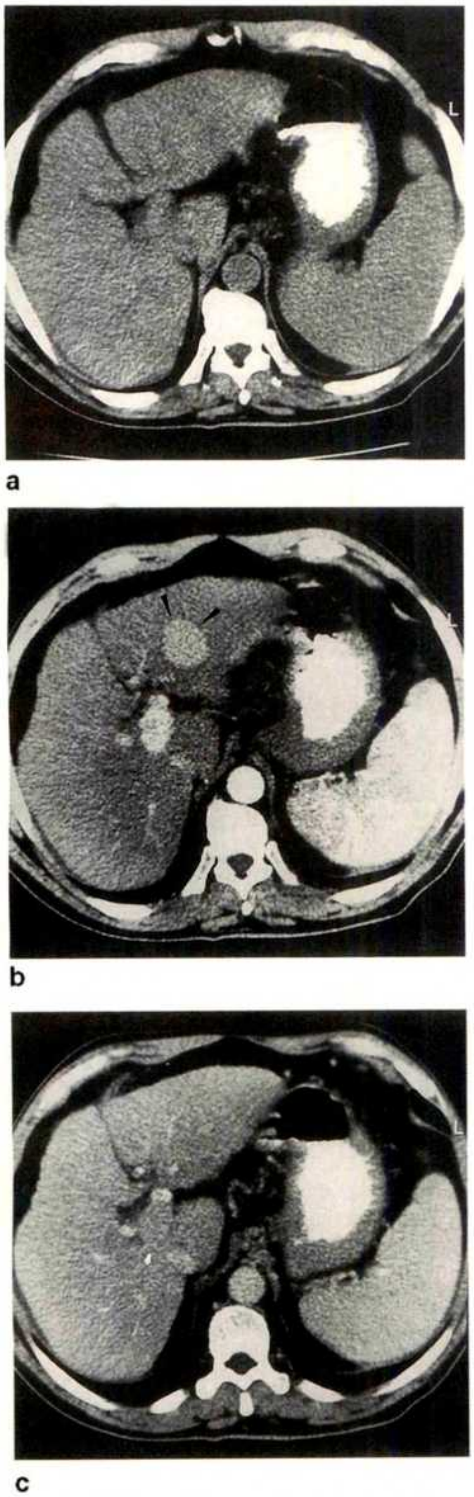

Fig. 1 Dual-phase helical computed tomography of hepatocellular carcinoma (HCC) in cirrhosis secondary to hepatitis B. **a** Unenhanced image shows no visible tumour nodule. **b** Hepatic arterial phase image, obtained 28 s after initiation of intravenous contrast administration, shows a 3·5-cm HCC demonstrating arterial enhancement (arrowheads) against the minimally enhanced liver parenchyma. **c** Corresponding portal venous phase image, obtained 70 s after initiation of infusion; the lesion is now isoattenuating (not visible) with hepatic parenchyma because of an equally intense liver enhancement

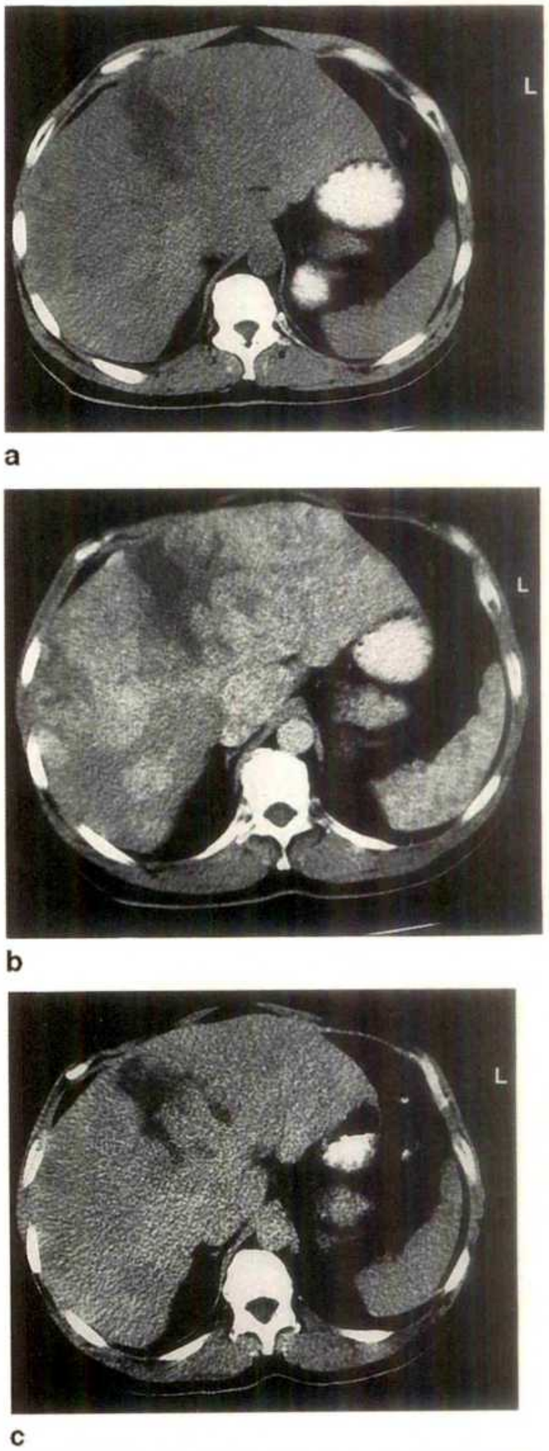

Fig. 2 Multifocal hepatocellular carcinoma in a patient with chronic hepatitis B. **a** Unenhanced and **c** equilibrium phase computed tomography images fail to visualize the exact extent of tumour which demonstrates dense enhancement and full conspicuity on the hepatic arterial phase image (**b**)

images respectively[57]. Siderotic nodules are more straightforwardly recognized by their low signal in both T1- and T2-weighted spin-echo images. In a recent study, however, data from thin-section MRI performed on fresh whole livers within 4 h of surgical explantation from 30 non-Asian patients were correlated with pathological findings.

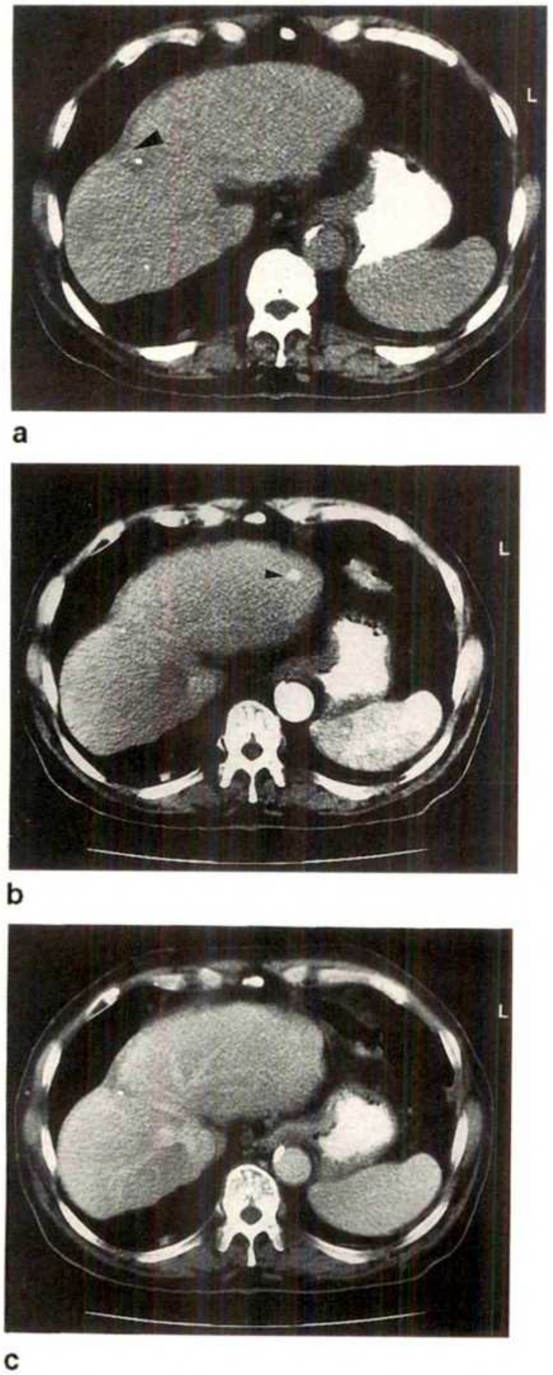

Fig. 3 Small hepatocellular carcinoma (HCC) in cirrhosis due to chronic hepatitis B. Two years before this scan, the patient underwent segmentectomy for a liver nodule which proved histologically to be a regenerative nodule. **a**, **b** and **c** Images from current dual-phase helical computed tomography of the liver. **a** Unenhanced image shows a scar (arrowhead) due to previous surgery and no tumour nodule. **b** Hepatic arterial phase image obtained at the same level as **a** shows a small nodule demonstrating intense homogeneous arterial enhancement (arrowhead). **c** Corresponding portal venous phase image shows no lesion because the tumour is now isoattenuating with the rest of the liver. The patient underwent liver transplantation and a small (1·2 cm) HCC was found in the left lateral segment of the explanted liver

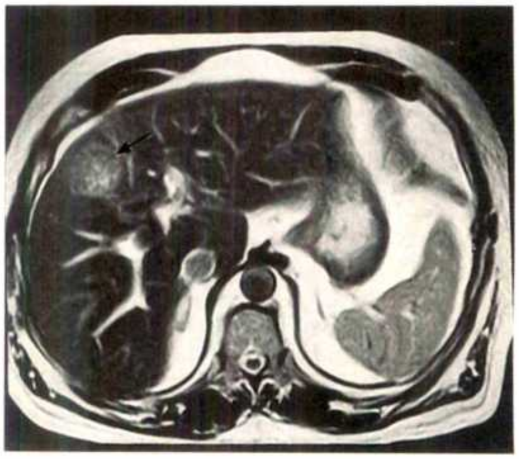

Fig. 4 Magnetic resonance image in a patient with chronic viral hepatitis B. Axial T2-weighted spin-echo image shows a hyperintense hepatocellular carcinoma in the right hepatic lobe (arrow)

The results challenge current concepts for the differentiation of benign from malignant nodules in cirrhotic liver based on MRI[58]. Signal intensity characteristics for HCC varied so much that distinction of a non-siderotic dysplastic nodule from HCC based on MRI was impossible. Detection of HCC by MRI can, of course, be helped by findings such as the presence of intratumoral fat or the demonstration of a capsule. Moreover, with improved gradient-echo sequences that allow breath-hold MRI of the whole liver during the HAP, PVP and equilibrium phase after intravenous bolus injection of extracellular gadolinium chylates, tumour detection and characterization can be improved. Finally, MRI of cirrhotic liver may be enhanced by the use of contrast agents exhibiting some specificity in their biodistribution within the liver, such as reticuloendothelial and hepatobiliary agents[59]. However, *in vivo* magnetic resonance images with limited spatial resolution, motion-related artefacts and a variety of signal intensity characteristics on T1- and T2-weighted images often make differentiation of cirrhotic liver nodules impossible. What is left at the present time is probably the identification of a clinical or molecular marker that can be used to recognize the nature of an individual dysplastic nodule.

Recent advances in the management of hepatocellular carcinoma

The heterogeneous aetiology, biological properties and presentation of HCC worldwide make it unlikely that a single method of treatment will ever be developed for universal application. Nevertheless, several common principles should be applied in designing treatment for individual patients. First, it is important to classify the patient into one of the acceptable scoring categories delineating the functional state of the liver disease using, for example, the Child–Pugh[60,61] or the Okuda[62,63] classification. Usually, patients with stage B/C or stage II and III disease in both scoring systems will not benefit from most forms of therapy. Second, if possible, surgical excision should be attempted in patients with Child–Pugh stage A or Okuda stage I lesions, when unifocal tumours are less than or equal to 5 cm in diameter, preferably encapsulated and with no evidence of portal vein invasion. However, it should also be remembered that a significant number of patients with Child–Pugh A or Okuda stage I disease develop transient or occasionally irreversible hepatic decompensation after surgery, despite an (over)optimistic preoperative assessment.

Non-surgical therapeutic modalities for hepatocellular carcinoma

The following discussion reviews the available conservative means of therapy mainly for patients with Child–Pugh A/B or Okuda stage I and II disease and briefly addresses the many experimental avenues currently being explored[30,64–104] (*Table 4*).

Systemic chemotherapy. Single-agent chemotherapy and combination chemotherapy have been claimed as effective in palliation of HCC. Among these agents the anthracycline derivative doxorubicin (adriamycin) was initially considered the most effective. However, the overall response rate to systemic administration of adriamycin is extremely poor. Meta-analysis of 13 studies in 644 patients treated with adriamycin revealed an overall response rate of 19 per cent with a calculated median survival of only 16 weeks[64]. The use of other chemotherapeutic agents, such as epirubicin and cisplatin, and combination therapies using adriamycin and 5-fluorouracil given systemically, or even through intra-arterial injection, have not improved these results significantly[64]. The risk of adverse events, including cardiac and bone marrow toxicity and activation of the multidrug resistance gene, weighs against the potential benefits following systemic administration of anthracyclines and hardly justifies their use. Thus, based on available data, currently there is no indication for systemic chemotherapy in patients with HCC until more efficacious and less toxic drugs become available.

Blocking of oestrogen receptors (hormone therapy). Several studies, some of them controlled, suggest a limited benefit of tamoxifen in prolonging survival of patients with HCC; others have not confirmed this effect. Insufficient drug dosage, altered abnormal oestrogen receptors and other factors may contribute to the variable effect of tamoxifen[73–78]. One study reported a 1-year survival rate of 35 per cent in 16 patients with unresectable HCC, compared with 0 per cent in matched controls[74]. Some physicians use this relatively benign form of therapy for palliation and (especially) reassurance of patients in whom all other forms of therapy are either not applicable or unsuccessful. Tamoxifen therapy is usually well tolerated although sometimes associated with fatty infiltration of the liver. A recent double-blind placebo-controlled clinical trial in 120 patients did not establish a significant effect of tamoxifen in HCC[77].

Transcatheter oily chemoembolization. Transcatheter oily chemoembolization (TOCE) involves selective injection into the hepatic artery feeding an HCC of a suspension (prepared on site immediately before the injection) containing a chemotherapeutic agent (adriamycin, cisplatin or mitomycin C) and Lipiodol (Lipiodol Ultra-fluid; Guerbet, Aulnay-Sous-Bois, France)[79]. The type of chemotherapy used for chemoembolization is a matter of individual policy and no clear-cut data suggest a benefit of one agent over the others. Nevertheless, some investigators prefer cisplatin[80–82]. Lipiodol, which contains iodine (38 per cent), is derived from the ethyl ester of the fatty acid in poppyseed oil and was originally used as a contrast lymphographic agent. Lipiodol has a selective 'affinity' for HCC tissues. The mechanism of Lipiodol retention in HCC is not completely understood, but may be related to mechanical trapping in the microvasculature of the tumour[83,84]. Recent work suggests that endothelial cells in HCC vasculature take up Lipiodol from the vessel lumen rapidly and pass it on to tumour cells directly or via an intratumoral transport network involving stromal components, such as Ito cells[105,106]. This property can be used with relative specificity for diagnostic as well as therapeutic purposes in HCC, and occasionally in fibrolamellar carcinoma or cholangiocarcinoma. However, some non-specific retention may occur in benign lesions in the liver, such as focal nodular hyperplasia and haemangioma, or at the site of a recent hepatic biopsy.

Once trapped in the HCC tissue, and providing that the feeding hepatic artery is occluded, Lipiodol is slowly released over a period of 6–12 weeks and even longer. Thus the emulsified preparation of Lipiodol and adriamycin or other agents can be used for targeting of HCC as a slow-release agent. Occlusion with Gelfoam

Table 4 Non-surgical treatment for hepatocellular carcinoma

Treatment mode	Comment	In clinical practice	Reference
Systemic chemotherapy	Practically abandoned	Yes/no	64
Hormone therapy-oestrogen receptor block	Palliative	Yes	73–78
Targeting modality			
Intra-arterial			
Transcatheter chemoembolization		Yes	30, 79–95
Radiolabelled Lipiodol injection	Experimental		96, 97
Percutaneous intralesional ethanol injection		Yes	98–103
Systemic intravenous adriamycin encapsulated in liposomes	Experimental		104
Immunotherapy			
Monoclonal antibodies		Experimental	70–72
Chemoimmunotherapy (conjugated with adriamycin)		Experimental	70–72
Radioimmunotherapy (radiolabelled and antiferritin; monoclonal or polyclonal antibodies)		Experimental	70–72
Systemic immunotherapy			
Interleukin 2		Experimental	70–72
Interferon alpha		Experimental	70–72

particles (Gelita Tampon; B/Braun, Melsungen, Germany) or (less desirably) with Gelfoam powder of the hepatic artery that feeds the tumour is believed to augment significantly the effect of Lipiodol–adriamycin (or cisplatin or mitomycin C), although occlusion alone may have an independent temporary effect. The procedure can be repeated every 2–4 months, alone or in combination with intralesional alcohol injection[85].

Most patients develop one or another form of postchemoembolization syndrome. This includes fever, abdominal pain, nausea, deterioration of liver function tests and hepatic decompensation, and (rarely) cholecystitis, hepatic encephalopathy, hepatic or splenic infarction, liver abscess and death[86]. Most patients tolerate the procedure well[87] and within 2–3 weeks after the intra-arterial injection are ready to return to their routine lifestyle. However, the procedure is expensive and requires 3–7 days in hospital.

There are quite a large number of reports, some of them controlled, on the palliative advantages of chemoembolization[30,65–69,71,85–95]. However, the few controlled clinical trials have been unable to prove any long-term benefit. In one recent trial survival of patients with HCC at 1 year was 62 per cent in the chemoembolization group and 44 per cent in controls (*P* not significant); tumour size was significantly smaller in the treated group[107]. Nevertheless, interpretation of results compared with control populations is exceedingly difficult for reasons mentioned above, especially in this study in which patients were recruited from 24 centres in three countries[107]. Those who advocate chemoembolization often make optimistic statements about the effect in individual patients. Indeed, despite a discouraging interpretation of results in some trials, a 41 per cent increase in estimated 1-year survival rate in treated patients compared with controls[107], although not statistically significant, appears clinically important. It is, however, wise to avoid as much as possible treating patients with Child–Pugh stage C or Okuda stage III disease. On the other hand, some patients with tumour diameters over 5 cm and with moderately decreased synthetic hepatic function do benefit from this procedure. In an unpublished series from Jerusalem (Shouval *et al.*) conducted in patients with Okuda stage I disease 6-month survival was reached in only 50 per cent of 36 untreated patients with HCC in 1984, compared with 13 of 27 patients treated with chemoembolization (using Lipiodol–adriamycin) between 1994 and 1996 who survived for 26 months or longer.

It is customary to order a follow-up CT scan of the liver at 2–3 weeks after TOCE to verify the selective uptake of Lipiodol in the tumour; if CT is done earlier, background staining of the liver can provide false information. Thereafter the slow release of Lipiodol from the original tumour site can be monitored at intervals of 4–6 weeks, with repeat CT (not requiring intravenous contrast infusion). When it disappears, a new session of treatment may be indicated. Repeated sessions of TOCE may lead to obliteration of the hepatic artery and are occasionally associated with miliary spread of the tumour within the liver or to the lungs. Lipiodol injection without adriamycin also can help in the diagnostic evaluation of an unidentified space-occupying hepatic lesion in a patient with chronic hepatitis in whom AFP levels are not raised, or whenever a liver biopsy is not feasible or acceptable to the patient. However, injection of Lipiodol alone may block the tumour site for a period of 2–4 months, so that repeat injection with Lipiodol–adriamycin suspension will not be possible until the original uptake of Lipiodol is cleared. Therefore there are physicians who immediately inject the Lipiodol–adriamycin emulsion even in the absence of definite histological proof of the presence of HCC, providing that the degree of suspicion is high enough to justify the procedure as, for example, in the presence of significantly raised levels of AFP in the setting of chronic liver disease and the presence of a space-occupying lesion within the liver. Another potential application of Lipiodol has been explored using ^{131}I-radiolabelled Lipiodol (without a chemotherapeutic agent) for hepatic intra-arterial injection in patients with HCC[96,97]. It is too early to assess the usefulness of this strategy.

Some surgeons perform chemoembolization before surgery or even before OLT in patients with tumours of less than 5 cm in diameter. This policy has several potential advantages, including the detection of unidentified additional HCC foci, and the induction of tumour cell lysis and tumour shrinkage. However, there is no clear-cut evidence that this approach improves the survival of patients who have undergone surgical resection and it may even shorten it[108–110].

Percutaneous intra-lesional ethanol injection. PEI is a relatively simple procedure in which absolute alcohol is injected into an HCC focus, usually less than 5 cm in size, using a specialized, CT-guided, multiporous fine needle. Repeated injections, sometimes on consecutive days, lead to coagulation and ablation of HCC foci, and to tumour cell necrosis. Success of treatment is assessed by the loss of intravenous contrast medium enhancement on CT, although treatment can also be done with ultrasonographic guidance. PEI has relatively few side-effects, which include pain, especially when alcohol is injected in subcapsular areas or when intraperitoneal leakage occurs. Tumour cell spread may also occur along the needle track. PEI may be as effective as surgical resection for small HCCs (less than 3 cm in diameter) and, in general, should be applied to lesions smaller than 5 cm in diameter, alone or in combination with chemoembolization[98–103]. A 3-year survival rate of 63 per cent for those with a single HCC lesion less than 3 cm in diameter has been reported[99], although the 5-year recurrence rate was high (87 per cent). Most of the recurrences do not involve the primary focus and so repeated injections during follow-up should be considered. Recently, percutaneous intravascular alcohol injection of the vessels feeding the tumour has been added to the experimental options for palliation of HCC[111].

Experimental modes of treatment: the future. In the past decade several new experimental methods have been developed for the treatment of HCC. These include administration of adriamycin trapped in liposomes[104], microwave therapy[112], percutaneous acetic acid injection[113], administration of an acyclic retinoid polyprenoic acid for prevention of second primary tumours[114], external or internal hepatic radiation[115], and even gene therapy in culture or experimental animals[116,117]. One of the most active avenues of research is the exploration of the various roles of immunotherapy[70] and, in particular, the role of immunotargeting[71,72]. The various experimental immunotargeting techniques include immunotherapy using monoclonal antibodies against tumour-associated antigens, given as free antibodies or conjugated to chemotherapeutic agents such as adriamycin. Another avenue is immunotherapy with polyclonal or monoclonal antibodies to ferritin, radiolabelled with iodine-131 or with yttrium-90[70–72]. The administration of interferon α, interleukin 2 or tumour necrosis factor has not so far met with significant success in a small number of pilot studies[70].

None of these new treatment modalities has so far been introduced into clinical practice. Nevertheless, a number of them may be potentially useful in palliation, especially in situations where surgical tumour debulking or liver transplantation are possible, and where eradication of residual tumour cells has a better chance after removal of the dominant tumour mass.

Surgical management of hepatocellular carcinoma

Surgical management of HCC has two arms, *non-resectional* procedures of local tumour destruction by devascularization, electrocoagulation, microwave or laser coagulation, cryosurgery or radiotherapy, and different types of conventional or extended liver *resection*, including techniques of inflow/outflow occlusion, *in-/ante-/ex situ* protection (modifications of the standard technique of liver resection with *in situ* protection by hypothermic perfusion or backtable work) or total hepatectomy and allotransplantation. Although this long and still incomplete list of therapeutic tools clearly emphasizes the present limitation in effective control of HCC on a wide scale, there is a definite chance of potential cure with complete surgical excision of all tumour tissue[118,119]. Assessment of prognosis after surgery has up to now been based on retrospective analyses in a few centres with sufficiently long experience. Thus it was shown that the overall outcome for any form of resectional surgery is significantly influenced by the patient's clinical condition and, especially, the pathological stage of the disease. Detection of early tumour at stage I and II, according to the tumour node metastasis classification of the Union Internacional Contra la Cancrum (*Table 5*)[120], followed by radical liver resection gives the best results, with a low operative mortality rate (5–10 per cent) and a 5-year actuarial survival rate of 60–70 per cent compared with more advanced disease (stage III and IV) for which the corresponding survival rate drops to 20–30 per cent or less[121,122].

Similar results may be expected with liver transplantation, although one must bear in mind that the two treatment modalities are not exactly comparable. There is a selection bias involved such that only patients with non-resectable and usually more advanced tumours are transplanted. One must also consider the influence of underlying parenchymal liver disease with the 'incidental' finding of small tumours. When considering patients with HCC in cirrhosis in particular, it is still not at all clear whether partial liver resection or transplantation is superior. There seems to be a survival advantage in patients who receive a liver allograft instead of partial hepatectomy, not only for late but also for early tumour stages. However, this is not yet proven by accurate statistical analysis in large series[123,124].

Since the overall resectability rate is low, new or extended surgical options must be examined. Whether the various modifications of *in-/ante-/ex-situ* 'bench' surgery with liver autotransplantation, total hepatectomy and liver allotransplantation or multivisceral 'cluster' resection will extend current limits of surgical resectability (and even more the limits of oncological radicality) is open for discussion[125].

Table 5 Tumour node metastasis staging system for hepatocellular carcinoma (from the Union Internacional Contra la Cancrum)

T primary tumour	
T_1	Solitary tumour 2 cm or less in greatest dimension *without* vascular invasion
T_2	Solitary tumour 2 cm or less in greatest dimension *with* vascular invasion
	Multiple tumours limited to one lobe, none more than 2 cm in greatest dimension *without* vascular invasion
	Solitary tumour more than 2 cm in greatest dimension *without* vascular invasion
T_3	Solitary tumour more than 2 cm in greatest dimension *with* vascular invasion
	Multiple tumours limited to one lobe, none more than 2 cm in greatest dimension *with* vascular invasion
	Multiple tumours limited to one lobe, any more than 2 cm in greatest dimension *with* or *without* vascular invasion
T_4	Multiple tumours in more than one lobe or tumour(s) involving a major branch of the portal or hepatic vein(s)
N regional lymph nodes	
N_0	No regional lymph node metastasis
N_1	Regional lymph node metastasis
M distant metastasis	
M_0	No distant metastasis
M_1	Distant metastasis

Stage grouping			
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_1	N_1	M_0
	T_2	N_1	M_0
	T_3	N_0	M_0
	T_3	N_1	M_0
IVA	T_4	N_{any}	M_0
IVB	T_{any}	N_{any}	M_1

Very recently several authors have controversially advocated the performance of OLT as a principle in patients with potentially resectable HCC in cirrhosis. The existing data used to support this view, and the concept that the oncological risk of a cirrhotic liver is better controlled by total instead of partial hepatectomy, still need to be confirmed by prospective trials. In this context the role of adjuvant therapy before, during and after surgery must also be further elucidated[126,127]. In the light of limited donor resources, such an aggressive approach has to be considered carefully, especially if recommended on a wide scale.

Discussion

Unfortunately only a small proportion of HCCs are amenable to surgical removal. Furthermore, once a malignant focus of HCC is identified and surgically excised or treated conservatively, the risk of developing another malignant focus remains in the majority of patients, in whom the inflammatory stimulation and cirrhosis continue to exist as background risk factors. Treatment for HCC is rarely curative; it should be regarded as palliative, even if eradication of the first focus seems successful.

Physicians who design a treatment strategy for HCC must take into account many factors, including the presence and the diameter(s) of unifocal or multifocal tumours, the existence of cirrhosis, the functional reserve of the liver, the degree of portal hypertension, the presence of hepatic encephalopathy, and the patient's age as well as his or her general condition. Furthermore, it is sometimes difficult to establish how differentiated the transformed liver cells are, their doubling time, and how fast the tumour will grow in the future. In general, partial liver resection is the management of first choice, especially for early tumour stages. It allows a good chance of long-term cure or at least of significant palliation with an acceptably low operative risk. When tumours are non-resectable because of anatomical restrictions (location, size or number of intrahepatic lesions) or functional impairment (underlying cirrhosis), OLT may be an alternative, as long as there is no malignant tumour growth outside the liver. For patients with relatively small and occasionally multiple tumours, who are not candidates for surgical excision or OLT, PEI and chemoembolization, separately or in combination, should be administered. This should be done according to individual centre experience until there are sufficient data on the efficacy of various protocols.

Since so many factors affect the prognosis of patients with HCC, it is still almost impossible to design well controlled clinical trials to assess new experimental modes of therapy. This is also the reason why many therapeutic modality trials, both old and new, use historical controls for comparison. However, future studies must concentrate on establishing the optimal therapeutic strategy for HCC, including multimodality protocols involving a combination of surgical and conservative measures. The only route to definite answers will be through prospective trials involving centres with a major interest in HCC. Such studies must compare different treatments on the basis of most accurate pathological tumour classification and staging; they must also acquire a sufficiently long follow-up.

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Review

Pseudomyxoma peritonei

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Background Pseudomyxoma peritonei is an unusual condition in which gelatinous fluid collections are associated with mucinous implants on the peritoneal surfaces and omentum. The pathological origin and ideal treatment of the condition are subjects of debate.

Methods An unrestricted Medline search over 1986–1997 was performed for pseudomyxoma peritonei.

Results and conclusions There is increasing evidence that pseudomyxoma peritonei is a neoplastic condition which usually arises from a primary adenoma or adenocarcinoma of the appendix. Reported series include a spectrum of pathological lesions, from entirely benign ruptured mucocele to advanced carcinoma. This, and the rarity of the condition, limit the conclusions that can be drawn regarding its treatment and prognosis. Most authorities agree that a thorough surgical debulking should be made. In most cases this will be a difficult and time-consuming undertaking, possibly requiring cooperation between two or more specialists and consideration of delivering intraperitoneal adjuvant therapy during or immediately after surgery. Treatment therefore requires a planned approach with accurate preoperative assessment of the diagnosis and the extent of the condition. There is some largely anecdotal evidence in favour of intraperitoneal chemotherapy and radioisotope treatment. Ultraradical surgery, with heated intraoperative and further postoperative chemotherapy, is strongly advocated by one group but remains contentious. The majority of patients will eventually suffer recurrence. The 5-year survival rate ranges from 53 to 75 per cent, but outcomes vary widely between relatively benign and malignant subgroups.

Pseudomyxoma peritonei is an unusual condition in which diffuse collections of gelatinous fluid are associated with mucinous implants on the peritoneal surfaces and omentum. It is two to three times more common in females than males and is said to be present in two of every 10000 laparotomies[1]; it is often an unexpected finding. The term 'jelly belly'[2] has been used to characterize the large accumulations of mucinous ascites that may be encountered at laparotomy.

A clinical case consistent with this diagnosis was first described by Rokitansky in 1842[3], but it was Werth[4] who first coined the term pseudomyxoma peritonei in 1884 when he described its occurrence in association with a mucinous carcinoma of the ovary. The term *pseudo*myxoma referred to chemical differences from other types of mucin that had been analysed. In 1901 Frankel[5] described it in association with a cyst of the appendix.

After these early descriptions, a debate arose about the significance of ovarian and appendiceal disease as the origin of pseudomyxoma peritonei. Simultaneous disease is found at these two sites in the vast majority of female patients with this condition. Recent applications of immunocytochemistry and genetic analysis by the polymerase chain reaction have made a major contribution to the resolution of this debate.

Pathological origin

The study of pseudomyxoma peritonei is limited by the rarity of the condition and the small number of cases collected in published series. Most of these series are retrospective and use differing inclusion criteria. They may be biased towards different types of disease process by presentation to surgical or gynaecological units.

Many gynaecological publications have emphasized the association with ovarian mucinous tumour of low malignant potential (MLMP), also termed mucinous borderline tumour. Standard textbooks have often simply accepted that any mucinous ovarian tumour present in a female represents the origin of the disease[6,7]. However, when the appendix is examined histologically, mucoceles, adenomas or carcinomas are found in nearly all cases. This simultaneous disease in most female patients might be explained either on the basis of spread from the appendix to the ovary or on the basis of two independent primary disease processes. If there is a single primary neoplasm other deposits should show features consistent with a clonal origin. If there is more than one primary neoplastic lesion a predisposing field change is implied. It has been suggested that this might arise because of mucinous metaplasia due to chronic irritation from ascitic fluid[8,9].

Many reports describe pseudomyoxoma peritonei in association with a ruptured mucocele of the appendix and do not mention neoplasia. Cheng[10] successfully reproduced mucoceles of the appendix by ligating the organ in rabbits, but subsequent sterile rupture of the mucoceles did not lead to pseudomyxoma peritonei. Carr *et al.*[11] have made an extensive clinicopathological study of tumours and tumour-like lesions of the appendix. In their 11 cases of simple mucocele, dissection of the wall by acellular mucin was frequently observed and three patients formed a localized collection of acellular mucin in the right lower

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quadrant. However, pseudomyxoma peritonei did not develop. It is now generally accepted that pseudomyxoma peritonei is due to neoplastic mucus-secreting cells within the peritoneal cavity. These cells may have low-grade cytological appearances and be sparsely distributed within collections of extracellular mucin, but they will invariably be identified when appropriate techniques are applied[12]. Carr[13] believes, because of the relentless growth of the cells, that pseudomyxoma peritonei should always be classed as a malignant condition irrespective of other histological features. However, there is no consensus of opinion on this matter. Nor is there agreement as to a point of separation between pseudomyxoma peritonei and carcinomatosis peritonei due to advanced, high-grade, mucinous carcinomas, which may also produce extracellular mucin within the peritoneal cavity.

Certain features of pseudomyxoma peritonei tend to support the hypothesis that most cases originate in the appendix with frequent secondary spread to the ovary. Proponents of this hypothesis point out that the ovarian tumours are either bilateral or else predominantly right-sided; only 20 per cent occur on the left side alone[14]. The histological appearances often suggest implantation of tumour on the surface of the ovary. Pseudomyxoma ovarii is the name given to the histological appearance of mucin dissecting through the stroma of the ovary. It is considered to be a feature of secondary ovarian tumours and is seen in 88 per cent of cases of pseudomyxoma peritonei but in only 25 per cent of uncomplicated ovarian MLMPs[15]. It is also pointed out that the appendix and ovary are unlikely to share a common predisposition to neoplasia when they have different embryological origins. Except in pseudomyxoma peritonei, it is extremely rare for appendiceal and ovarian neoplasms to occur simultaneously.

Those who believe that the ovarian disease is usually a primary process argue that the low histological grade of the ovarian lesions would be surprising for a metastasizing neoplasm. They also point to the fact that metastases to other solid organs are extremely rare in pseudomyxoma peritonei.

In 1993 Seidman *et al.*[15] argued strongly that pseudomyxoma peritonei represents 'multifocal neoplasia of the peritoneum, ovary and appendix'. They supported this view with a study of 15 cases of pseudomyxoma peritonei with ovarian and appendiceal disease. Specimens from both sites were tested with four immunoperoxidase stains. One representative block each from the ovarian tumour and the appendiceal tumour were evaluated, together with a representative block from a deposit in the omentum or peritoneum. Concordance of staining was demonstrated in only five of 15 cases. Kahn *et al.*[16] and Kaern *et al.*[17] also favoured the concept of multiple primary tumours arising because of a field change in the tissues concerned. They drew similar conclusions from clinical and histological data. However, Young *et al.*[14] criticized Seidman's conclusions, noting that heterogeneity of immunohistochemical staining is not uncommon within the same tumour. One of their own studies[18] analysed clinical and histological features in 22 cases of pseudomyxoma peritonei with both appendiceal and ovarian disease; they concluded that the ovarian tumours were probably secondary to primary appendiceal lesions. Prayson *et al.*[19] reached the same conclusion from analysis of 17 similar cases.

Ronnett *et al.*[20] defined criteria for the diagnosis of secondary ovarian involvement and found that these were satisfied in 28 of 30 cases of pseudomyxoma peritonei. No case of unequivocal ovarian origin was identified. Recent immunohistochemical findings have added strong support to the theory that most, if not all, tumours associated with pseudomyxoma peritonei originate from a primary in the appendix. Ronnett *et al.*[21] performed a study based on the fact that nearly all ovarian MLMPs and mucinous carcinomas stain positively for cytokeratin (CK) 7, 18 and 20, as well as carcinoembryonic antigen (CEA) and human alveolar macrophage (HAM) 56; most colorectal adenocarcinomas are positive for CK 20 and CEA but negative for CK 7 and HAM-56. In 13 cases of pseudomyxoma peritonei, appendiceal mucinous adenomas and ovarian tumours from the same patient were stained for these antigens. In ten of 13 cases the staining patterns were identical at the two separate sites. In eight of these cases a typical 'colorectal' pattern of staining was demonstrated. In two of the remaining patients with identical staining patterns at the two sites, the pattern was 'colorectal' except for a positive CK 7. The typical colorectal pattern was also seen in the ovary of an additional case with no appendiceal specimen. A control group of ovarian MLMP tumours was then analysed. The frequency of immunopositivity for CK 7 and HAM-56 was significantly different between the two groups, with the ovarian tumours in pseudomyxoma peritonei tending to be negative for CK 7 and HAM-56, and so similar to the appendiceal tumours. This was in marked contrast to the findings from the control group of ovarian MLMP tumours. These authors concluded that most ovarian tumours in pseudomyxoma peritonei are immunophenotypically identical to associated appendiceal tumours and distinct from primary MLMPs. Two smaller cytokeratin studies[22,23] were inconclusive but not inconsistent with this conclusion. Cuatrecasas *et al.*[24] used the polymerase chain reaction to study *c-Ki-ras* mutations in ovarian and appendiceal tumours from patients with pseudomyxoma peritonei. Identical mutations were present at the two sites in all six cases studied.

A dissenting voice has, however, been sounded by Chuaqui *et al.*[25], who found some heterogeneity in genetic microsatellites from similarly paired specimens. These authors concluded that second primary tumours were present in some cases.

In addition to discussion of pseudomyxoma peritonei in association with appendiceal and ovarian tumours, the literature also contains sporadic case reports of associations with tumours of the colon and rectum[26], lung[27], breast[28], pancreas[29], stomach[26,30], gallbladder and bile ducts[31], fallopian tubes[32,33] small intesine and urinary bladder[26]. Another report has attributed the disease to retained rectal tissue after proctectomy[2].

Both case reports and collected series of pseudomyxoma peritonei represent a heterogenous group of pathological lesions. Ronnett *et al.*[12] suggested that some may have little in common other than the production of abundant extracellular mucin. Because of the considerable variation in applying different pathological terms, they proposed that pseudomyxoma peritonei be defined as 'a clinicopathological entity characterized by mucinous ascites and non-invasive mucinous implants with a characteristic distribution and containing histologically benign mucinous epithelium derived from an appendiceal mucinous adenoma and having a benign clinical course'. Cases fitting this definition were to be labelled as having 'disseminated peritoneal adenomucinosis', whereas similar cases, but with malignant histological features, were to be classified as 'peritoneal mucinous carcinomatosis'. In their painstaking study of 109 patients they also required an intermediate group for 14 cases that could not be allocated satisfactorily to either of these categories. Helpful as these definitions are, no other groups have yet adopted them in published studies of pseudomyxoma peritonei.

Clinical presentation and investigation

In series published to date, pseudomyxoma peritonei has usually been an unexpected diagnosis made at laparotomy. The preoperative diagnosis has often been one of appendicitis or an ovarian tumour. The most commonly recorded symptoms have been abdominal pain, distension or a mass in the abdomen. Nausea, vomiting, fatigue and urinary symptoms have also been described[20,34], as well as presentation with a scrotal mass[35]. In one series[36] more than 25 per cent of patients presented with the finding of mucinous tumour in the sac of a hernia.

At operation, a variable volume of mucinous ascites has been found, together with tumour deposits that typically involve the right hemidiaphragm, the right retrohepatic space, the left paracolic gutter and the ligament of Treitz. The peritoneal surfaces of the bowel are usually free of tumour[37]. The appendix is usually abnormal and one or both ovaries may be involved. The formation of bulky secondary disease from a small primary has been termed a 'redistribution phenomenon'[37]. The sites of predilection may reflect mucin production, absence of adhesion molecules on the pseudomyxoma cells, peristalsis of the intestines, gravity and the presence of open lymphatic lacunae on the omentum and undersurface of the diaphragm[37].

Imaging

Many reports refer to cases discovered before ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI) were used regularly in the investigation of abdominal complaints. Most other articles on imaging in pseudomyxoma peritonei are based on reports of three or four cases. Many such reports continue to be quoted years after publication to validate statements on the findings of imaging in this condition[38–41]. The sensitivity and specificity of these findings have never been assessed objectively and are never likely to be because of the rarity of the condition. The most substantial account of imaging in pseudomyxoma peritonei comes from Walensky *et al.*[42] who described 33 patients from the Johns Hopkins Hospital in Baltimore, Maryland, USA, who had at least one of the following studies: plain radiography, barium studies, ultrasonography, CT or MRI. Regrettably, the numbers assessed by each modality are not stated for the last three modalities.

Imaging before surgery is highly desirable, as a preoperative diagnosis allows the operation to be planned and performed by a surgeon with the necessary time, facilities and skills to carry out radical debulking and institute intraperitoneal adjuvant treatment, where appropriate. It is also valuable in the assessment of recurrent disease.

Plain radiography and contrast studies. Plain films are generally considered unhelpful for diagnosis but may show central displacement of the intestines and obliteration of the psoas shadows[42,43]. Rarely, punctate, annular or curvilinear calcifications are seen within the gelatinous masses in pseudomyxoma peritonei[44].

Radiography with contrast media was performed in 21 cases in the Baltimore series[42] and in new cases invariably demonstrated the lack of bowel lumen involvement that is characteristic of the relatively non-invasive deposits found in pseudomyxoma peritonei. Barium enema also served to exclude colorectal tumours and to assess large bowel obstruction, particularly in recurrent disease.

Ultrasonography. Ultrasonography is frequently employed and typically shows non-mobile echogenic ascites with 'scalloping' of the hepatic and splenic margins due to extrinsic pressure of adjacent peritoneal implants[41,42]. The echogenic texture may be interspersed with areas of hypoechogenicity. The echogenicity of the ascites corresponds with semisolid gelatinous masses and the walls of tiny mucinous cysts[40]. Early experience with endoscopic ultrasonography has also been reported[45].

Computed tomography. CT is now widely employed to establish the diagnosis and extent of pseudomyxoma peritonei[42]. The mucinous material is similar in density to fat and appears heterogeneous[2]. Scalloping of the liver, spleen and mesentery are easily demonstrated together with central displacement of bowel loops. The occasional calcifications mentioned in connection with plain radiography are also seen on CT. Sugarbaker *et al.*[36] use two features of the CT scan to make a preoperative distinction between peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. The presence of tumour greater than 5 cm on the jejunum, proximal ileum or adjacent mesentery is said to indicate either a mucinous adenocarcinoma or impaction of adenomucinosis within the abdomen and pelvis. Focal narrowing of small bowel loops with segmental obstruction indicates peritoneal adenocarcinomatosis. None the less, Hameed *et al.*[46] wrote a cautionary case report of a patient with endometriosis who was wrongly suspected of having pseudomyxoma peritonei despite CT.

Magnetic resonance imaging. There are even fewer data on MRI, the application of which is limited by expense and poor availability of equipment. The authors from Baltimore[42] failed to mention how many MRI scans were performed on their patients. The same morphological features seen on CT can be demonstrated on MRI. Buy *et al.*[39] have reported that T2-weighted images provide optimal contrast from normal tissue. They also stated that MRI may be particularly sensitive for the detection of visceral invasion but their conclusions are based on the study of three cases.

Cytology and frozen-section histology

A number of authors have studied the cytological appearances of peritoneal aspirates from patients with pseudomyxoma peritonei[47–52]. Between two and nine patients form the basis of these reports. Direct smears and smears from centrifuged or filtered material were used. These authors agree that the aspirates typically contain much mucus and few cells. The mucus stains positively with periodic acid–Schiff, astra blue, mucicarmine and alcian blue. The mucin is typically clumped in a network of slender, benign-looking cells which have the appearance of fibroblasts. In the marginal areas of the clumps and around them, plump, rounded 'mesothelial' cells are seen. Malignant cells are not frequently noted and will not necessarily be identified even when a histological diagnosis of carcinoma is subsequently made. Typical appearances were not identified in all of the cases reported and, in some, they could be identified only after retrospective review of the cytological material. From these reports, it is impossible to assess the sensitivity and specificity of aspiration cytology in the diagnosis of pseudomyxoma peritonei. Hence, its value in clinical practice remains uncertain.

Frozen section has sometimes been employed for rapid histological assessment of operative biopsies. However, this method may make it particularly difficult to separate the microscopic appearances from those of endometriosis[53].

Tumour markers

Zoetmulder and Sugarbaker[54] advocate the measurement of CEA levels but do not report any data on levels in their patients. A few authors have retrospectively reported the levels of CEA and CA19-9 in very small numbers of patients[47,55]. These anecdotal data indicate only that levels of CEA and, perhaps CA19-9, are not infrequently raised in patients with pseudomyxoma peritonei and may rise in association with recurrent disease. In a report of four patients with pseudomyxoma peritonei and mucinous ovarian tumours, three also had a raised CA125 level[56].

Treatment

No active treatment

Friedland *et al.*[57] argued that active treatment was not necessarily desirable in pseudomyxoma peritonei. Their paper described a single patient whose abdominal distension was believed to have increased asymptomatically for 5 years before diagnosis. No follow-up after diagnosis was mentioned. They asserted that patients with pseudomyxoma peritonei survive for many years with few problems. However, the only supporting evidence cited is an old textbook and an article[58] that actually describes survival after radical surgery.

Surgery

Thorough surgical debulking is widely regarded as the mainstay of treatment in this condition[19,34,59–61]. As far as possible, all gross disease should be removed. The appendix should also be removed for histological assessment.

Ultra-radical surgery and adjuvant treatment. Sugarbaker, who has published extensively on pseudomyxoma peritonei, advocates a particularly rigorous surgical approach which involves systematic excision of affected peritoneal surfaces with diathermy. He has published a clear and well illustrated account of the relevant techniques[62], which in certain sectors of the abdomen involve routine excision of the gastric antrum, rectosigmoid colon or gallbladder. In addition, a right hemicolectomy is frequently performed. Using these techniques with adjuvant intraperitoneal and systemic chemotherapy, Sugarbaker *et al.*[63] claimed excellent results in a series of patients with pseudomyxoma peritonei. However, for the reasons discussed above, it is impossible to be certain that these patients are fully comparable with those in other series. Gough *et al.*[34] have drawn attention to the high complication rate and short follow-up in the published data of Sugarbaker and co-workers.

More recently Sugarbaker *et al.*[36] have published an updated account of their series, which now includes at least 131 patients; an exact figure cannot be quoted because of inconsistencies within the tabulated data in that report. The separation of patients into groups with adenomucinosis, mucinous carcinoma and intermediates allows them to highlight an excellent 5-year survival rate of 80 per cent in their best pathological group, but the present authors calculate that the overall 5-year survival rate for all pathological categories is only 60 per cent, which is barely better than the historical figures from the Mayo Clinic reported by Gough *et al.*[34]. This being the case, it is particularly unfortunate that Gough *et al.*'s median survival and 5-year survival rates are substantially misquoted in their paper[36]. The paper discusses operative morbidity and mortality for 138 patients whose peritonectomy operations took a mean of 11 h and involved a mean blood loss of 1700 ml and a mean of 2·5 intestinal anastomoses. The overall mortality rate was 2·7 per cent but no timescale was defined. This rate rose to 5 per cent with their most recent practice of giving intraoperative intraperitoneal chemotherapy heated to 44°C, but the difference was not statistically significant. The overall complication rate was 36·1 per cent. Nine per cent of patients had pulmonary complications that were not described in any more detail; all other complications were major. The mean duration of ileus was 19·3 days. While Sugarbaker and co-workers are to be respected for their commitment to treating this disease and for their unique prospective collection of data on the condition, it is impossible to be sure that the complexity and complications of their techniques are justified. There is no valid control group with which their results can be compared. They attract many patients by tertiary referral whose prognosis may be better or, indeed, worse than those presenting to other centres.

Mucolytic agents

Green *et al.*[64] were the first to advocate the use of dextrose solution to loosen the mucinous deposits. Other authors have been enthusiastic about the use of this and other suggested mucolytic substances[65,66], both as an aid to operative cytoreduction and as a means of obtaining closed catheter drainage of mucinous material for palliation. However, a laboratory study[67] failed to demonstrate any mucolytic advantage of 5 per cent dextrose and some other solutions when compared with normal saline. Furthermore, a recent report[68] described an incident of potentially fatal hyperglycaemia due to the use of dextrose for peritoneal lavage.

Phototherapy

Sindelar *et al.*[69] have produced a detailed technical description of the use of photosensitizers and laser light as an adjuvant to conventional dissection at laparotomy for disseminated peritoneal malignancy, including pseudomyxoma peritonei. Unfortunately, the article does not begin to address the question of its efficacy as a treatment for pseudomyxoma peritonei. As with hyperthermia (see below), phototherapy suffers from obvious technical difficulties, potential complications and lack of proven clinical benefit.

Chemotherapy and intraperitoneal hyperthermic chemotherapy

While some authors are enthusiastic about the results they have obtained with adjuvant chemotherapy[36,70], reports are essentially anecdotal. No formal trials have been conducted, even against historical controls. Therefore, there are no hard data to establish the benefits of adjuvant chemotherapy in this condition.

Many agents have been tried either as systemic treatment or as intraperitoneal infusions during or after surgery. The most widely used have been 5-fluorouracil (5-FU), cyclophosphamide and mitomycin C for intraperitoneal treatment, and 5-FU, cyclophosphamide, L-phenylalanine mustard and doxyrubicin for systemic treatment. Cisplatinum, which is known to be effective in ovarian cancer, has been used by both intraperitoneal and systemic routes. Interestingly, it is not clearly beneficial in pseudomyxoma peritonei[1].

In the Mayo Clinic series[34], retrospective review showed that survival was significantly more likely in patients given intraperitoneal chemotherapy and less likely in those given systemic chemotherapy. However, this result might have been due entirely to selection bias. In the series from the Memorial Sloan-Kettering Cancer Center[71] there was no significant difference in survival between similarly compared groups given and not given chemotherapy.

Most recent work has focused on intraperitoneal delivery of chemotherapy, with particular interest in the use of solutions heated to temperatures of around 44°C. The theoretical benefits of such treatment for peritoneal carcinomatosis from appendiceal and colorectal cancer have been well elaborated by Sugarbaker[72]. The pharmacokinetics of intraperitoneal chemotherapy indicate that high concentrations of agents such as 5-FU and mitomycin C can be delivered to peritoneal tumour deposits without producing toxic systemic levels[73,74]. Penetration is particularly effective in superficial tumour deposits that have not invaded deeply from the peritoneal surface. Pseudomyxoma peritonei should, in theory, be ideally suited to this treatment, particularly as bloodborne and lymphatic metastases are uncommon in this condition. Interest in using hyperthermic solutions arises from *in vitro* studies indicating that they may be more cytotoxic to tumour cells than solutions at body temperature[75–77].

There is some direct evidence that intraperitoneal chemotherapy produces improvement in the histological appearance of residual deposits of disseminated colorectal and appendiceal carcinoma resampled at a second laparotomy[78]. Changes are distributed patchily throughout the abdomen, presumably due to the difficulty of delivering an even application of the treatment. This has led one exponent of the technique to change from giving intraperitoneal chemotherapy solely in the postoperative period to starting it during operation, when it can be manually swilled around the peritoneal cavity, albeit with a somewhat demanding technique to avoid spillage[36]. The results for various peritoneal tumours treated by Sugarbaker's group[79] and work on gastric cancer from Japan[76] indicate that adjuvant intraperitoneal chemotherapy is associated with a better outcome if a complete surgical cytoreduction has been achieved.

While conclusive evidence for the use of adjuvant chemotherapy may be difficult or impossible to obtain in a rare condition such as pseudomyxoma peritonei, its further study will be encouraged by the results of a limited trial of adjuvant hyperthermic chemotherapy in peritoneal carcinomatosis secondary to gastric cancer[80]. This showed a significant survival advantage for patients so treated, 31 per cent of whom survived for 5 years.

Radiotherapy

The Mayo Clinic series[34] produced a survival advantage for patients treated with intraperitoneal radioisotopes, but, as mentioned above, this was only a retrospective comparison of non-randomized groups. The isotopes ^{32}P and ^{198}Au have been used in this context. External-beam radiotherapy has been used in the past for primary adjuvant treatment and for recurrences[81–83], but has obvious drawbacks in the abdomen and is associated with substantial morbidity. Early experience with radioimmunotherapy for solid cancers has been reviewed by Kairemo[84], who reported a few cases of pseudomyxoma peritonei treated in this way in his department.

Treatment of recurrent disease

At the benign end of the disease spectrum, pseudomyxoma peritonei is a disease that progresses slowly and in which recurrences may take years to develop or become symptomatic. Jahne *et al.*[85] have described a low rate of perioperative morbidity, even after multiple relaparotomies, and therefore argue for surgical treatment of recurrent disease. Surgery for recurrent pseudomyxoma peritonei is usually difficult because of adhesions and fibrosis, greatly increasing the risk of unintentional enterotomies and subsequent leaks and fistulas. However, it is widely accepted that recurrences should be investigated vigorously and treated with further surgical debulking, with or without adjuvant chemotherapy, in the expectation that many patients will enjoy substantial additional survival and freedom from symptoms.

Outcome

The study of mortality and disease recurrence in pseudomyxoma peritonei is confounded by the small number of patients collected with adequate follow-up data, and the fact that different series have different inclusion criteria that may bias their populations towards more or less aggressive extremes of the disease.

Recurrence

The median follow-up period of 12 (range 9–25·6) years for surviving patients in the Mayo Clinic series[34] is considerably better than in most other reports of pseudomyxoma peritonei. Seventy-six per cent of patients ultimately developed recurrence and 50 per cent of recurrences occurred within 2·5 years. If the debulking procedure excised all viable tumour, symptomatic recurrence occurred later than after a subtotal debulking (mean 2·6 *versus* 1·9 years). Of the 38 patients requiring a second operation because of recurrence, 24 went on to a third operation and 15 to a fourth procedure. The timescale of the further recurrences and the lengths of survival after recurrence is, unfortunately, not clear from this paper. At the Massachusetts General and Brigham and Women's Hospitals[60], the total recurrence rate was 52 per cent in 23 patients, but a shorter period of follow-up was reported. Sugarbaker *et al.*[36] reported that approximately one-third of their patients required reoperation for recurrent adenomucinosis. This was presumably the recurrence rate in their best prognostic group of patients with disseminated peritoneal adenomucinosis.

Complications

Primary pseudomyxoma peritonei usually causes little interference with the function of the abdominal organs even when there is considerable bulk of disease. As with other pelvic tumours, obstruction of venous return from the lower limbs has been reported[83], as has ureteric obstruction[86]. Recurrent disease is much more likely to occur on the bowel surfaces[54] and is regularly associated with intense fibrosis and adhesions. For this reason, intestinal obstruction and obstructive jaundice are common and are often a cause of death in pseudomyxoma peritonei. Metastases to lymph nodes and to the parenchyma of solid organs are unusual and nearly always represent disease due to a relatively high-grade mucinous carcinoma.

Survival

Median survival of 5·9 years, and 5- and 10-year survival rates of 53 and 32 per cent respectively were reported for 56 patients collected between 1957 and 1983 at the Mayo Clinic[34]; equivalent figures for 17 cases of pseudomyxoma peritonei 'of appendix origin' at the Memorial Sloan-Kettering Cancer Center were 6·25 years, 75 and 10 per cent[71]. If the disease is subclassified it becomes clear that survival is considerably worse in patients with more malignant clinical and histological features. When Ronnett and colleagues[12] subdivided their cases into 'disseminated peritoneal adenomucinosis' and 'peritoneal mucinous carcinomatosis' they were able to report a 5-year survival rate of 84 per cent in the former and 6·7 per cent in the latter group, with 33·6 per cent in an intermediate group. Similarly, workers at Sacramento have reported a 3-year survival rate of 80 and 4 per cent respectively for patients with non-invasive and invasive deposits[26].

Conclusions

Recent applications of immunocytochemistry and studies of genetic material using the polymerase chain reaction have increased the likelihood that most cases of pseudomyxoma peritonei are due to metastases from neoplasms of the appendix. Because of the rarity and heterogeneity of the condition, there is little hard evidence regarding optimum treatment, but expert opinion favours radical surgical debulking with or without adjuvant intraperitoneal chemotherapy or radioisotope treatment. The majority of patients develop recurrent disease at widely varying intervals after the original diagnosis. Further debulking is then indicated, but this is likely to be difficult owing to fibrosis, adhesions and possible intestinal obstruction. Five-year survival rates of 50–70 per cent are to be expected.

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Review

Acute non-traumatic arm ischaemia

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Background Much attention has been paid to the management of acute leg ischaemia. Acute arm ischaemia is perceived as less of a problem because the risk of limb loss is lower. After conservative treatment up to half the patients have late symptoms, such as forearm claudication.

Methods This study was a review of all published English language data on acute arm ischaemia. The entire Medline database was searched and other references were derived from the material perused. There were no randomized or controlled studies.

Results The incidence of acute arm ischaemia is one-fifth that of acute leg ischaemia. Patients with arm ischaemia tended to be older with a mean age of 74 years compared with 70 years for acute leg ischaemia. Since the development of the embolectomy catheter, embolectomy can be performed in most patients under local anaesthetic. Collected outcome included successful restoration of the circulation in 65–94 per cent of patients and amputation in 0–18 per cent. The mortality rate ranged from 0 to 19 per cent, despite the use of local anaesthesia, mostly from associated cardiac disease. Management by a vascular specialist may be beneficial, particularly in complex cases.

Conclusion An active approach to the management of acute arm ischaemia is safe and effective and reduces the risk of late disabling symptoms.

Acute ischaemia of the arm is uncommon compared with events in the leg. However, the consequences of impaired function or amputation of an arm are devastating, with loss of independence and/or livelihood[1,2]. Individual events of acute arm ischaemia are not as limb-threatening as those in the leg and thromboembolectomy is not always required for limb salvage. There is considerable controversy about how aggressively acute arm ischaemia should be treated, particularly when the arm appears viable.

This review examines the evidence on acute arm ischaemia based on English language publications reported in Medline (entire database). Fewer than 50 significant publications exist and there are no randomized trials. Clinical data are limited to reviews (including up to 260 patients) derived from a range of sources, including district general hospitals, regional centres and specialist vascular units. These cover intervals before and after the introduction of the embolectomy catheter and consider disparate patient populations. All the identified articles on acute upper limb ischaemia have been included in the present review, except case reports. This review observes how management strategies have developed and attempts to draw some guidelines for the treatment of acute ischaemia of the arm.

Acute arm ischaemia can be caused by intrinsic thromboembolism or trauma. Brachial artery injury secondary to cardiac catheterization is now probably the commonest cause of direct arterial injury requiring surgery[3]. The incidence of this problem is less than 1 per cent of all brachial cardiac catheterizations and may be falling. Nevertheless the number of procedures is increasing (more than 100 000 per year in North America[3]), and so cardiac catheterization will continue to be an important cause of arm ischaemia.

Traumatic injury to the arm arteries is rare and there is little information on the relative incidence compared with intrinsic arm ischaemia. Lambert *et al.*[4] reported 37 patients who required emergency surgery for acute arm ischaemia over 5 years. Of these, 56 per cent of episodes were caused by cardiac catheterization, 24 per cent were due to emboli and 20 per cent to stab wounds. In this small series arterial injury secondary to bony fracture was not mentioned. Katz and Kohl[5] reported 65 patients who had surgery for upper limb ischaemia over 8 years. Fifty-four (83 per cent) presented acutely, 41 per cent with emboli of cardiac origin, 17 per cent with emboli from other peripheral arteries, 15 per cent with traumatic ischaemia and 28 per cent with an iatrogenic occlusion (mainly cardiac catheterization). In a hospital series of 31 patients with severe arm ischaemia from 1969 to 1978, Schmidt and Hewitt[6] classified the causes as follows: emboli (ten patients), thrombosis (six), trauma (six), catheter trauma (four) and other causes including Raynaud's disease, rheumatoid vasculitis and thoracic outlet syndrome (five). In a similar review, Quraishy *et al.*[7] described 57 patients with severe, but not necessarily acute, arm ischaemia from 1980 to 1989. The causes included small vessel arteritis (28 per cent), embolism (23 per cent), trauma (16 per cent), large vessel arteritis (12 per cent), atherosclerotic disease (10 per cent), thoracic outlet syndrome (7 per cent) and other (4 per cent). Trauma is responsible for between 15 and 45 per cent of cases of acute arm ischaemia. The following review discusses only non-traumatic arm ischaemia.

Clinical details

Incidence

The incidence of acute ischaemia of the arm is usually described as a proportion of the total number of episodes

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of acute ischaemia of the extremities. On review of the literature, acute arm ischaemia accounts for a mean of 16·6 (range 7–31·5) per cent of cases of acute ischaemia of the limbs[1,8–46].

In population surveys, the incidence of all types of limb ischaemia has been reported to vary between 7 and 21 per 100 00 per year[1]. This can be extrapolated to give a total incidence of acute arm ischaemia of 1·2–3·5 per 100 000 per year. Pentti *et al.*[1] reported 97 arm thromboembolectomies over 26 years in an unselected population of 430 000, an incidence of 0·86 per 100 000 per year. As in many other surgical series, these authors excluded patients with acute arm ischaemia who did not have an operation. Dryjski and Swedenborg[39] reviewed all patients with acute arm ischaemia presenting to hospital during 1 year and found an incidence of 1·13 per 100 000. The accuracy of published data for the incidence of acute arm ischaemia is questionable as most information comes from hospital or surgical reviews but, in the absence of a well designed population study, these figures provide the only available estimate.

Patients

There is a slight female preponderance in both observational and operative series. The mean age of patients with acute arm ischaemia was 67 years, slightly higher than the mean of 62 years in studies that included leg ischaemia. Stonebridge *et al.*[45] compared acute ischaemia of the arms and legs, and confirmed that patients with arm ischaemia tended to be older (74 *versus* 70 years).

Aetiology

Several well recognized problems confound investigation of the cause of acute arm ischaemia. Atherosclerosis is rare in the arteries of the upper limb, leading some investigators to label all non-traumatic ischaemia as embolic. While this may seem a reasonable assumption, it fails to distinguish the rarer causes of arterial occlusion such as *in situ* thrombosis. Furthermore, successful surgical disobliteration by balloon catheter is often taken to confirm the diagnosis of embolism and it is sometimes assumed that a failed procedure implies non-embolic disease. Most studies attribute the cause of embolism to associated cardiac conditions but often this cannot be confirmed pathologically. For example, a history of ischaemic heart disease can be enough for some to label an occlusion as embolic. Thus, assessment of the cause of ischaemia is biased by preconceptions about the aetiology of vascular disease of the upper limb; rare conditions, such as arteritis, can be missed completely. The following causes of acute arm ischaemia have been described.

Embolism. Embolism is considered the most common cause of acute arm ischaemia, accounting for between 74 and 100 per cent of cases[5,39,47,48]. Most investigators use some or all of the following criteria in the diagnosis of embolic ischaemia: sudden clinical presentation, an embolic source, absence of peripheral atherosclerosis and removal of discrete 'clot' at operation. The emboli are attributed to a variety of sources (*Fig. 1*).

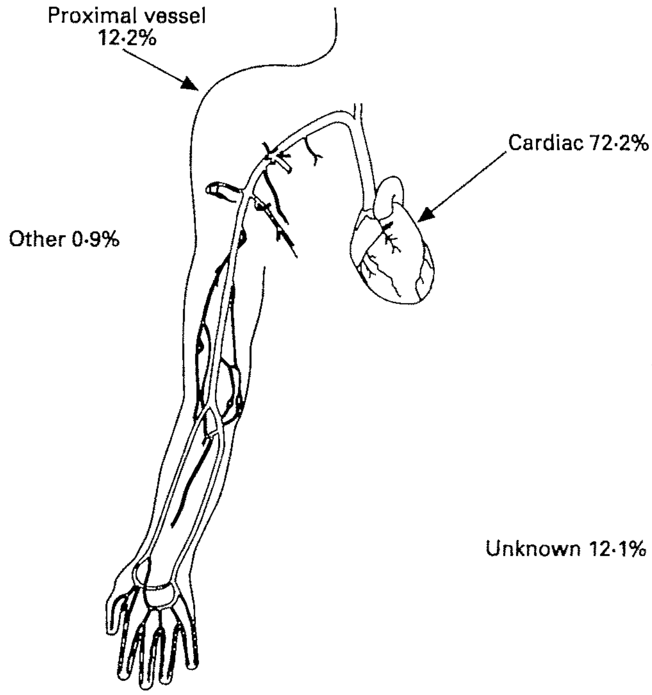

Fig. 1 Sources of brachial artery embolism taken from collected series[1,30,45,47,49–55]

Cardiac embolism is the most frequently reported cause of acute arm ischaemia, ranging from 58 to 93 per cent. Atrial fibrillation is the usual aetiology. Over the years the incidence of atrial fibrillation has remained fairly constant, although the cause of fibrillation has changed from valvular heart disease as a result of rheumatic fever to ischaemic heart disease and myocardial infarction. The myocardium can be a source of embolism even in the absence of atrial fibrillation or ischaemic heart disease. Rare causes include atrial myxoma[20,53], ventricular aneurysm[50], cardiac failure[50] and paradoxical embolism[56].

A significant proportion, ranging from 1 to 32 per cent, of acute arm emboli can be attributed to non-cardiac sources. Proximal upper limb arterial stenosis caused by atherosclerotic plaque[57–60] or external compression (e.g. cervical ribs[51,59]), can result in thromboembolism[58,59] or atheroembolism[60] which may cause large vessel occlusion or, more commonly, acute digital ischaemia. Other non-cardiac sources of embolism include atheroma in the aortic arch[47,50], primary subclavian aneurysm[51] or aneurysm secondary to extrinsic compression from thoracic outlet obstruction[58–61], old fracture[50,59,61] and chronic trauma such as that from the use of crutches[50]. Rarer sources include the proximal end of an occluded axillofemoral graft[5,36,58], arteritis[51], malignant emboli[33,62] and fibromuscular dysplasia[63].

Despite a classical embolic presentation and/or operative findings, an embolic source may not be found. Elliott *et al.*[34] noted, even with persistent searching using complex investigations, that a source of emboli could not be found in 11 per cent of patients.

Thrombosis. The true incidence of thrombosis as a cause of upper limb ischaemia is difficult to determine for the aforementioned reasons. Reports suggest that 5 per cent of cases in population studies and 9–35 per cent in surgical series are due to thrombosis[39,47,48]. The diagnosis is important because treatment usually requires bypass surgery, and inappropriate embolectomy or thrombectomy is associated with high morbidity and mortality rates[64,65]. Jivegard *et al.*[65] estimated that, in patients who had an embolectomy, the chance of thrombosis being the true cause was 5·5 per cent in the arm and 39 per cent in the leg. Most of the proximal arterial lesions that can cause emboli can also result in thrombosis, including atherosclerotic plaques, aneurysms[58] and arteritis[51]. The more proximal the lesion, the more likely it is that thrombosis is the cause of the acute ischaemia, especially if there is evidence of previous distal embolization. Less common causes include arteritis from connective tissue disorders[7], radiation[7,51,58], hyperthrombotic conditions[55] and thrombosis associated with malignancy or steroid use.

Other causes. Although Raynaud's phenomenon can present with severe upper limb digital ischaemia, the clinical picture is usually chronic and medical treatment is required. The importance with respect to this review is that proximal arterial lesions may present with Raynaud's-like symptoms due to microemboli[60].

Site of occlusion

The commonest sites of upper limb arterial occlusion are the axillary and brachial arteries, consistent with the likely sites for embolic occlusion (*Fig. 2*)[66,67]. Comparison between studies is difficult because some record the site of occlusion based on clinical findings whereas others include operative findings and angiography, where available. Acute ischaemia is slightly commoner in the right arm, which may reflect the proximity of the brachiocephalic artery to the heart[1]. In studies of thrombotic occlusion of the upper limb, the subclavian and axillary arteries tend to be favoured, presumably as a result of the associated causes[6,7,47,48,58].

Management

The greatest controversies about acute ischaemia of the arm relate to management. Once again the data are skewed by the fact that most reports are operative series; patients successfully managed conservatively are ignored. Reports which additionally include conservatively managed patients tend to come from vascular surgery units but most patients with arm ischaemia are almost certainly treated conservatively on medical or geriatric wards. Furthermore, data are influenced by the age of the series. Since Fogarty *et al.*[68] reported the technique of balloon catheter embolectomy in 1963, this has become the mainstay of surgical treatment for brachial emboli. Embolectomy is simple and can be performed under local anaesthesia. Development of balloon catheter embolectomy initially resulted in increased referral to surgeons and an increase in active treatment for acute arm ischaemia.

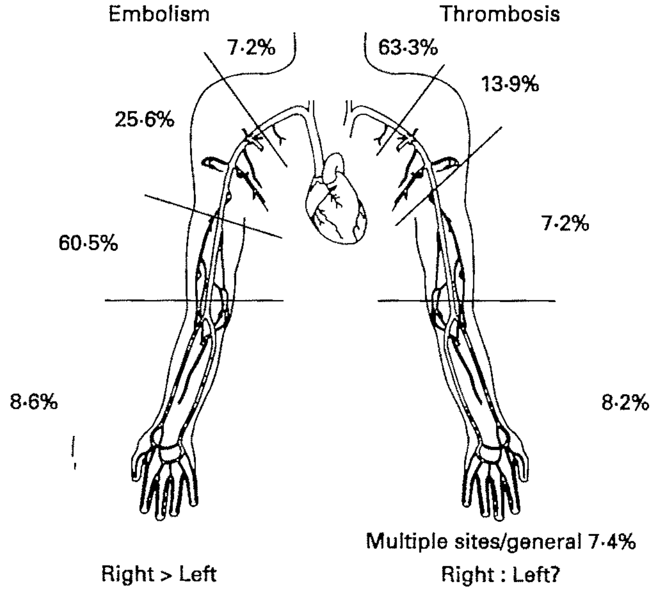

Fig. 2 Site of upper limb arterial occlusion from collected series according to cause of ischaemia[10,11,20,22,24–26,30,32,34,36,37,39–41,45,46,48,49,51–55,66,67]

Conservative treatment

Before embolectomy became routine, available treatment included warming the contralateral hand, chemical vasodilatation, anticoagulation, stellate ganglion block[47] and surgical sympathectomy[49]. Baird and Lajos[49] reported a series of 95 patients in 1964, before use of the embolectomy catheter was widespread. Seventy-eight were treated conservatively, 56 with supportive therapy and 22 with anticoagulation and sympathetic nerve block. Of these 78 patients, 68 per cent had a good result with no residual effect. However, 24 per cent had only a 'fair' outcome with residual weakness and/or arm claudication, while 8 per cent required amputation or had a useless limb[49]. This 'reasonable' outcome, coupled with the difficulty of effective surgical embolectomy at the time and the recognized superior collateral circulation of the arm, led to the continued recommendation of conservative treatment for acute arm ischaemia[12,69,70]. This opinion persists in some areas today, despite the introduction of balloon catheter embolectomy.

Modern series report that between 9 and 30 per cent of referred patients are treated conservatively[20,30,45,49–52]. Conservative therapy currently includes anticoagulation with heparin, rehydration, bed rest and treatment of contributing medical conditions, such as cardiac failure or dysrhythmia. Other non-surgical methods sometimes used are sympathectomy and, if indicated by angiography, angioplasty or thrombolysis. Patients treated conservatively in contemporary series have either mild symptoms or a serious medical condition which precludes surgical intervention even under local anaesthesia. Unfortunately, outcome reports seldom consider these patients separately. Savelyev *et al.*[30] described 47 patients with acute arm ischaemia treated conservatively because the ischaemia was not limb-threatening, or because of poor medical condition, or because the patient refused surgery. Only one patient subsequently developed gangrene, confirming that most had mild ischaemia. However, of those surviving to be discharged home, 75 per cent had functional impairment. This finding was supported recently by Galbraith *et al.*[40], who noted that 50 per cent of patients treated conservatively were left with forearm claudication. Kretz *et al.*[52] and Ricotta and co-workers[51] both reported a good outcome in 64 per cent of patients treated conservatively, and Sachatello and colleagues[50] denied residual symptoms in any of a small number of patients. Baird and Lajos[49] found that 32 per cent of patients managed conservatively were left with reduced function of the arm. Follow-up in many studies is limited and a proper functional assessment of outcome was seldom undertaken. However, these experiences have led many vascular surgeons to adopt an aggressive policy of embolectomy for all except the sickest patients in order to preserve full function of the arm[71].

Surgical treatment

Embolectomy is the most frequently performed surgical procedure for acute arm ischaemia. Occasionally, non-viable digits may require amputation. Outcome of surgery is generally reported as superior to that of conservative treatment, although direct comparison is impossible as the treatments are never chosen randomly. Published studies suggest that a favourable outcome can be expected in 65–94 per cent of patients treated surgically (*Table 1*). The mortality rate after embolectomy ranges from 0 to 19 per cent and in the majority of cases is due to associated cardiac disease or further embolization. Amputation of the arm for gangrene is seldom necessary. In 256 patients, Savelyev *et al.*[30] reported 25 cases (10 per cent) of gangrene; 12 of these patients required amputation and the remainder died. More recently, Panetta *et al.*[41] reported an amputation rate of 4·3 per cent after arm embolism.

Before 1963, surgical embolectomy involved arteriotomy and removal of the clot directly by 'milking out'[49] or by the use of suction catheters, corkscrew wires and specially designed forceps[30–32]. Arteriotomies were often necessary at multiple sites and therefore general anaesthesia was routine. Using direct arteriotomy, Baird and Lajos[49] reported a good outcome with no residual symptoms in 88 per cent of cases following embolectomy by direct arteriotomy, but only 18 per cent of the patients in their series had surgery. The introduction of the Fogarty balloon catheter in 1963 revolutionized the treatment of acute limb ischaemia[68]. The balloon catheter technique enabled complete removal of clot in most cases through a single arteriotomy and could be performed under local anaesthesia. Hence it was available for many more patients[35]. Satiani *et al.*[31] have recommended that all patients with acute arm ischaemia and a clinically obvious source of embolism should have urgent embolectomy. Preoperative angiography should be reserved for patients in whom the clinical features are not clearly diagnostic of embolism[31,47,51].

Most clinicians commence anticoagulation with heparin to prevent propagation of thrombus immediately the diagnosis of acute arm ischaemia has been made, particularly when there may be a delay before surgery[15,24,40,41,50]. Freund *et al.*[72], however, found no difference in the rate of limb salvage whether or not heparin was given before operation. Heparinization has been shown to benefit patients with acute leg ischaemia, and by extension most would agree with Kaar *et al.*[53] that preoperative anticoagulation should be routine.

Embolectomy

Satiani *et al.*[31] and others[54] have recommended that surgery be performed as soon as possible after correction of electrolyte balance and attention to any associated medical conditions. Savelyev and co-workers[30] noted a reduction in limb salvage and poorer subsequent limb function as the interval between onset of symptoms and surgery increased. Others have also noted the deleterious effect of duration of ischaemia[1,20,28,30,32,34,47,52–54], possibly because delay allows secondary thrombosis of small distal vessels which cannot be reopened by embolectomy[53]. These findings are a strong argument against a policy of 'anticoagulate and wait and see' for potentially non-viable arms. However, even when presentation is delayed, embolectomy is a worthwhile procedure if the ischaemia is not yet irreversible[20,24,28]. An arm that remains viable for several days after embolization usually has an intact distal circulation, enabling restoration of flow by embolectomy[20,31]. In advanced ischaemia embolectomy has been recommended to enable a more distal amputation, but this carries the risk of reperfusion injury and myoglobinuria[20,24]. Satiani *et al.*[31] suggest that fasciotomy should accompany embolectomy where the duration of ischaemia is over 48 h. However, the fascial compartments in the arm are lax and compartment syndrome is rare. In addition, general anaesthesia is usually required for fasciotomy.

Most embolectomies can be performed under local anaesthetic[33,40,53–55]. General anaesthetic is reserved for poorly compliant patients or for complex vascular reconstructions. However, even when local anaesthesia is used, an anaesthetist should be available in the operating theatre to monitor the patient, to treat any medical instability (particularly when the arm is revascularized), to administer sedation if required and to convert to general anaesthetic if necessary[2,42].

Now that embolectomy can usually be performed through a single arteriotomy, an antecubital fossa incision is preferred to mid-brachial and axillary sites, providing easy access proximally and to the two main forearm vessels. Sachatello *et al.*[50], and more recently others[4,33,55], have advised exposure of the bifurcation of the brachial artery to allow direct embolectomy of the radial and ulnar arteries. This is supported by Beckingham *et al.*[73], who

Table 1 Outcome following embolectomy for acute arm ischaemia

Reference	Year	No. of patients	Good outcome (%)	Amputation or symptoms (%)	Died (%)
Sachatello *et al.*[50]	1974	20	65	20	15
Savelyev *et al.*[30]	1977	105	76	5	19
Ricotta *et al.*[51]	1983	44	79·5	7	13·5
Kretz *et al.*[52]	1984	140	85	8	7
Galbraith *et al.*[40]	1985	25	84	12	4
Kaar *et al.*[53]	1989	51	76·5	15·5	8
Stonebridge *et al.*[45]	1989	50	94	0	6
Vohra and Lieberman[55]	1991	36	81	8	11
Davies *et al.*[54]	1991	36	89	11	0
Pentti *et al.*[1]	1995	97	80	18	2

were able to cannulate only one artery of the forearm on 42 per cent of occasions using a brachial arteriotomy and a conventional embolectomy catheter. A transverse incision in the brachial artery is preferred to prevent narrowing when the arteriotomy is repaired. When proximal passage of the embolectomy catheter fails to restore the inflow, exposure of the axillary artery is suggested to facilitate more direct embolectomy[2].

The result of the embolectomy is commonly assessed clinically by observing restoration of the radial and ulnar pulses with signs of improved cutaneous circulation. Failure to restore the radial pulse is a strong indicator of poor outcome[4,31,47,74]. In this situation, peroperative angiography should be performed to identify any residual occlusion, and treatment options include repeat embolectomy, exposure of the distal radial and ulnar arteries with retrograde embolectomy and flushing[50], and the use of intraoperative thrombolysis[41,75]. Routine peroperative angiography is not necessary (unlike in the leg), but it is worthy of note that in a study of postembolectomy angiograms 23 per cent showed evidence of residual thromboembolus or a technical error[31].

Long-term anticoagulation should be routine after embolectomy[34,50,54], unless there are medical contraindications, particularly when the heart is the source as there is a high risk of recurrent embolism[20,27,51]. Anticoagulation not only reduces the rate of recurrence, but also reduces postoperative mortality[27,34]. Anticoagulation is not required when the embolus has arisen from a clearly defined proximal arterial lesion such as a subclavian stenosis which has been treated effectively by angioplasty. Davies *et al.*[54] reported six patients, none of whom developed recurrent embolism 5 years after resection of a subclavian aneurysm despite withholding anticoagulation. Recurrent embolism has a higher mortality rate and a poor outcome for the arm. Panetta and colleagues[41] reported that recurrent embolism was more likely when the original cause was acute myocardial infarction, despite anticoagulation.

Following successful embolectomy for acute arm ischaemia it is questionable whether the source needs to be identified. When long-term warfarin therapy has been instituted and the source was clinically obvious, further investigation is not worthwhile. However, if there are any residual signs of diminished vascular supply, odd clinical features or no obvious embolic source, further investigation may be beneficial. Echocardiography may detect intracardiac thrombus or abnormality. Angiography or, more recently, colour duplex imaging of the upper limb vessels may identify a proximal stenosis as a source of platelet emboli. Treatment of these underlying causes is as important as anticoagulation therapy.

Other surgical treatment

In all cases, relief of acute ischaemia is the primary aim. This can usually be achieved by embolectomy, but when the source of emboli is a proximal arterial lesion definitive surgery or angioplasty may be required, either at the same time as embolectomy or later. Acute ischaemia due to thrombosis has a poor outcome if treated by simple catheter thromboembolectomy and is more likely to require reconstructive surgery. Such surgery should be tailored to the particular cause. An atherosclerotic stenosis of the subclavian or axillary artery is increasingly managed by angioplasty, with or without stenting[76]. The development of endoluminal technology may allow percutaneous treatment of proximal aneurysms[77]. Occasionally, surgical bypass may be required if angioplasty is unsuccessful. Proximal lesions can be dealt with by endarterectomy, anatomic or extra-anatomic grafting, while reversed vein bypass to distal arm arteries is effective for selected distal occlusions[5,6,47,58,59,78].

Extrinsic compression, particularly at the thoracic outlet by cervical rib or constricting band, can be the cause of occlusion or distal embolism. Vascular thoracic outlet compression is a clear indication for relieving surgery[79]. Poststenotic subclavian aneurysms may require resection and grafting to prevent recurrent embolism[58]. The timing of surgery or angioplasty designed to remove the cause of embolism in an otherwise viable limb is a matter for debate. While such surgery can be delayed, recurrent embolization is associated with a much worse outcome for the arm and a high mortality rate[51].

Thrombolysis

Peripheral thrombolysis has become established in the management of leg ischaemia[80], yet few reports describe its use in the arm. The limb salvage rate is much lower in acute ischaemia of the leg than in the arm, so there is more to gain and the risks of peripheral thrombolysis (approximately 5 per cent chance of major haemorrhage and 2 per cent risk of stroke) are justified[80]. In addition, catheters situated in the upper limb arteries for thrombolytic perfusion may lie adjacent to the origin of the carotid and vertebral arteries. Pericatheter thrombosis[81] or 'whirlpool embolism'[82] caused by injudicious forced perfusion of an occluded brachial artery can result in stroke. There is a perception among experienced radiologists that the risk of stroke is higher in upper limb thrombolysis and this is supported by the present authors, who have noted a higher rate of litigation. Nevertheless, thrombolysis has been used successfully for acute ischaemia of the arm[83] and may be particularly useful when distal vessels, which are less likely to be opened by brachial embolectomy, are occluded. Peroperative thrombolysis is well established following failed femoral embolectomy and may also be used in the arm[75].

Digital embolism (acute blue finger) may be an indication for thrombolysis but in most cases the fingers remain viable. Identification and treatment of the underlying cause to prevent recurrent embolization is more important. Widlus *et al.*[84] reported nine episodes of thrombolysis to treat acute upper limb ischaemia with concomitant balloon angioplasty in four. Iloprost, (Schering, Berlin, Germany) a synthetic prostanoid, has been used as an intravenous infusion to improve digital ischaemia[85] and has fewer potentially fatal side-effects than thrombolysis.

Discussion

Information about acute arm ischaemia is far too limited to allow firm guidelines on management. There remains much to be learned that can come only from careful population studies to assess the true incidence and natural history of the condition. Follow-up studies are also needed to determine the true outcomes of conservative and surgical management policies.

Based on the analysis of papers in this review, the authors offer the following comments on the management of acute arm ischaemia. An active surgical approach should be encouraged unless the patient is medically unfit. At presentation, all patients should be anticoagulated with heparin, unless contraindicated, and referred to a vascular surgical team. Although there is no direct evidence that this is advantageous, specialist vascular surgeons have been shown to improve the outcome for patients with acute leg ischaemia[86]. In addition, registries employed by many vascular surgeons may enable information to be collected about this condition.

Provided the patient is fit enough (and most should be able to tolerate surgery under local anaesthesia) embolectomy should be carried out as soon as possible in those with an obvious embolic source and evidence of neuromuscular dysfunction. If there is any doubt about the outcome after embolectomy, peroperative angiography should help identify the problem and permit the use of additional techniques such as peroperative thrombolysis or vascular reconstruction. Anticoagulation with heparin followed by lifelong warfarin therapy should be routine. Patients with an 'atypical' presentation should be considered for further investigation with angiography or duplex imaging.

In patients with no neuromuscular impairment, a period of heparinization can be undertaken before surgery[64]. This is particularly valuable for patients with correctable cardiac disease, or in those with thrombosis or an atypical presentation for whom further investigation (such as angiography) may be helpful.

In conclusion, although the published data are very limited, there is a significant incidence of residual disability following conservative treatment of acute ischaemia of the arm. Although limb loss and death are less likely outcomes following acute arm than acute leg ischaemia, a more active surgical approach in the arm might reduce late sequelae.

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Review

Lymphatic mapping and sentinel node biopsy in breast cancer

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Background Sentinel lymph node biopsy is a recently developed, minimally invasive technique for staging the axilla in patients with breast cancer. It has been suggested that this technique will avoid the morbidity associated with more extensive axillary dissection. A wide range of different methods and materials has been employed for lymphatic mapping, but there has been little consensus on the most reliable and reproducible technique.

Methods This is a comprehensive review of all published literature on sentinel node biopsy in breast cancer, using the Medline and Embase databases and cross-referencing of major articles on the subject.

Results and conclusion Sentinel node biopsy is a valid technique in breast cancer management, providing valuable axillary staging information. The optimal technique of lymphatic mapping utilizes a combination of vital blue dye and radiolabelled colloid. However, there remain controversial issues which require to be resolved before sentinel node biopsy becomes a widely accepted part of breast cancer care.

In the UK, around 26 000 new cases of breast cancer are diagnosed each year[1]. Currently, standard surgical management comprises resection of the primary tumour (whether by mastectomy or breast-conserving surgery) and axillary lymph node dissection. This allows clearance of the primary tumour and accurate staging of the axilla. Histopathological examination of the lymph nodes retrieved is currently the gold standard for axillary staging. This review examines the literature on a recently developed, minimally invasive technique of axillary staging.

In recent years breast surgery has become progressively more conservative; surgeons have moved away from radical mastectomy towards breast-conserving operations. The extent of axillary dissection remains controversial[2]. There are several important considerations that must be taken into account when performing axillary surgery: what is its value in terms of prognostic information, does it provide local control of disease, and does it offer any survival benefit?

Clearly, not all women have axillary metastases. However, in a series of 24 740 patients with breast cancer, the overall incidence of metastatic disease in the axilla was 46 per cent[3]. For tumours of 1 cm in diameter or less, the incidence of axillary nodal metastases ranges from 3 to 22 per cent[4–6]. There is overwhelming evidence that axillary lymph node involvement is the most important prognostic factor in patients with breast cancer[3,7]. Thus, axillary dissection will always be an important staging procedure, yielding information for the planning of adjuvant therapy.

In the absence of local treatment to the axilla with either surgery or axillary radiotherapy, the risk of axillary recurrence is high. Non-randomized studies have revealed an axillary recurrence rate of 19–21 per cent[8,9]. Patients in the National Surgical Adjuvant Breast and Bowel Project-B04 trial were randomized to either axillary surgery or no axillary surgery[10]. Of those who had no axillary surgery, 19 per cent subsequently developed regional recurrence within 10 years. However, 35 per cent of patients randomized to no axillary surgery did in fact have some degree of axillary dissection[11]. In light of this, the true incidence of axillary recurrence in patients who had no nodes removed was 21 per cent[12]. The time taken for axillary recurrence to become clinically apparent may be prolonged[10] and further patients in this group may have died from distant metastases before developing clinically detectable axillary disease. The implication from this is that the majority of patients with axillary metastases will at some stage go on to develop clinical disease in the axilla if not treated.

Following complete axillary dissection, the risk of recurrence is 1–3 per cent[10,13–15]. When axillary sampling is performed, there is a risk that inadequate surgery will understage the axilla[8,16–18]. Consequently, patients who are node positive will go unrecognized and untreated, leading to increased axillary recurrence rates[13]. Axillary sampling has been evaluated in this regard in several studies. Forrest *et al.*[19] described a sampling technique in which a minimum of four nodes are retrieved from the axilla. Using this technique, it was found that axillary recurrence rates were not significantly different from those in patients who had axillary clearance following mastectomy[20] or breast-conserving surgery[21]; patients who had positive nodes on axillary sampling were treated with axillary radiotherapy. In a further study from Edinburgh[22], axillary sampling was performed and the patient then randomized to either axillary clearance or no further surgery. In 67 patients who underwent axillary clearance following sampling, none converted from node-negative to node-positive status following the more extensive procedure.

A larger study from the Danish Breast Cancer Group[23] of 13 851 patients found that those with more than ten negative nodes retrieved from the axilla had significantly better axillary recurrence-free survival, overall recurrence-

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free survival and overall survival than if fewer than ten nodes were removed. These conflicting findings serve to highlight the risk of false-negative staging of the axilla following sampling as opposed to clearance. Finally, perhaps the largest of the issues surrounding axillary surgery is whether any overall survival benefit accrues from the procedure. This remains a controversial topic, about which there is much disagreement[2,24,25]. It has recently been reviewed comprehensively elsewhere[26].

There is potentially significant morbidity attached to the procedure of axillary dissection[27]. Arm lymphoedema is generally accepted as one of the principal complications of axillary surgery[28–30], although one randomized trial has reported that lymphoedema was not a prominent problem following either axillary sampling or dissection[31]. It has been suggested that the risk of lymphoedema increases with the extent of surgery[32], although an Edinburgh study[31] did not confirm this finding, nor did a non-randomized study from Yorkshire[13]. However, it has been demonstrated repeatedly that axillary surgery plus radiotherapy increases the risk of lymphoedema[13,15,28,29], although this difference was not significant in the Edinburgh study[31]. Lymphoedema may predispose to cellulitis, and has been shown to have psychological side-effects[33]. Potentially the most significant but extremely rare complication of arm oedema is the development of lymphangiosarcoma, the Stewart–Treves syndrome[34].

Neuropathies may also occur following axillary surgery. Intercostobrachial nerve syndrome (paraesthesia of the axilla, shoulder and upper arm) has been reported[35]. In a series by Lin *et al.*[32] 78 per cent of patients complained of paraesthesia in the distribution of the intercostobrachial nerve and 47 per cent also complained of pain. After axillary dissection, shoulder movement may be restricted[27], a problem that may be compounded by radiotherapy[31]. Seromas may occur in 10–52 per cent of women following surgery, despite the use of suction drains[36]. Finally, early postoperative complications such as haematoma, wound infection and delayed wound healing are also seen[37–39].

Given such morbidity, there is clearly an incentive to avoid axillary surgery in women who are lymph node negative. Currently, the only accurate method of identifying women with positive axillary nodes is histopathological examination of all lymph nodes removed at axillary dissection. Clinical examination has been shown to be unreliable in demonstrating the presence of axillary metastases[40]. Ultrasonography has also been employed to determine axillary nodal status[41] but, although it is more accurate than clinical examination, its reported sensitivity of 73 per cent renders it an inadequate method of non-invasive staging. Computed tomography has been shown to have no higher a yield than basic investigations[42]. Magnetic resonance imaging has also been studied in assessing the axilla but, with a reported sensitivity of 90 per cent for axillary metastases[43], it remains inferior to surgical staging. Positron emission tomography is a technique that has been used with some degree of success in the detection and staging of breast cancer[44–46]. However, this is an expensive method, which is currently a research tool.

The sentinel lymph node

Recent techniques have been developed to allow the identification of positive regional lymph nodes without clearing the whole lymphatic basin. The concept of the sentinel lymph node (SLN) was originally introduced in 1977 in the management of penile carcinoma[47]. This states that the first lymph node to receive lymphatic drainage from the site of a tumour should be the first site of lymphatic spread. Therefore, a tumour-free SLN implies the absence of lymph node metastases in the entire lymphatic basin.

In penile carcinoma, lymphatic mapping to identify the SLN was performed using lymphangiography. The concept of SLN biopsy was then introduced to patients with cutaneous melanoma by Morton and colleagues[48]. The approach in this study was to inject 0·5–1·0 ml of blue dye intradermally at the site of the melanoma. This allowed intraoperative identification of blue-stained lymphatic vessels leading away from the primary tumour to the blue SLN.

The techniques used for intraoperative lymphatic mapping in this study were based on previous work in a feline model by the same group[49]. The feline study examined several vital blue dyes and concluded that isosulphan blue was the most useful for lymphatic mapping. Isosulphan blue is the monosodium salt of 2,5-disulphonated triphenyl methane. It is weakly bound to albumin and is taken up selectively by the lymphatics[50]. Other dyes, examined by Wong *et al.*[49], were abandoned as they gave unsatisfactory results. Methylene blue, a water-soluble dye, proved to have poor lymphatic uptake and caused background staining of the tissues. Cyalume, a fluorescent dye, was also examined and, while it allowed good visualization of the lymphatics, it leaked out into the interstitial tissue space, resulting in marked background fluorescence. For this reason isosulphan blue was chosen as the best agent for lymphatic mapping, as it rapidly enters the lymphatic vessels and is readily visualized in the vessels and SLN, with minimal diffusion into the soft tissues.

In studies of the technique in patients with melanoma, Morton *et al.*[48] compared isosulphan blue with patent blue-V. Patent blue-V is a triphenyl methane similar in structure to isosulphan blue. These workers found that patent blue-V gave optimum results in visualizing the lymphatics, and postulated that this may be because of its greater concentration (2·5 per cent in aqueous solution compared with the 1 per cent concentration of isosulphan blue). In this initial report, Morton *et al.*[48] commented that injection of large volumes of dye resulted in extravasation in the subcutaneous tissues, with consequent movement of dye through separate lymphatic channels, and so advocated the use of small volumes (0·5–1·0 ml). Furthermore, they noted that, if dissection was not performed promptly, dye would pass through the sentinel nodes up to higher lymph nodes in the regional basin. This caused fading of the colour and to avoid this repeat injection of the dye was performed every 20 min.

In Morton's series of 237 patients[48] a sentinel node or nodes was identified in 194 cases (82 per cent). In all, 72 per cent of patients had a single SLN, 20 per cent two SLNs and 8 per cent three SLNs. The study also showed that there is a learning curve associated with this procedure; as surgeons become more experienced, their rate of SLN detection increases significantly. Of the 194 patients who had a sentinel node identified, 40 (21 per cent) had lymph node metastases. Two patients in this group of 194 had metastatic deposits in non-sentinel nodes in the absence of tumour in the SLN; thus the false-negative rate was 1 per cent. It is of interest that in the 40 patients with lymph node metastases, 23 were detectable using haematoxylin and eosin staining techniques, but a further 17 were only detectable using immunohistochemistry. In all cases, the SLN was the only site of metastatic disease.

Further work has validated this approach in patients with melanoma[51]. By demonstrating in a series of 42 patients that none had skip metastases, Reintgen *et al.* provided evidence for the theory that nodal metastasis in melanoma occurs in an orderly fashion. In addition, in the eight cases where there were nodal metastases, seven occurred in the SLN alone, providing further evidence in support of the sentinel node hypothesis.

The use of vital blue dyes, such as isosulphan and patent blue-V, in lymphatic mapping for melanoma has some drawbacks. It may be difficult to visualize or to dissect out the blue-stained lymphatic vessels and nodes in the lymphatic basin. The site of the SLN is unknown before surgery and it may be difficult to site the incision accurately for exposure of the SLN. Furthermore, dye may pass rapidly to non-sentinel nodes, resulting in the staining of several nodes and preventing the true sentinel node from being found. In an attempt to avoid these pitfalls, some groups have advocated radionuclide techniques[52–55].

Lymphoscintigraphy to demonstrate lymphatic drainage patterns and to identify the SLN in melanoma has been described in several studies[52–57]. Preoperative scintigrams allow identification of the SLN and marking of its position on the overlying skin. A γ probe can then be used at operation to identify the 'hot' SLN during dissection. Initial studies in a feline model found that the sensitivity of SLN identification was the same as that for vital blue dye[58]. The reliability of the technique was verified in a small study of ten patients with melanoma, and the use of preoperative lymphoscintigraphy and intraoperative use of the γ probe were considered to allow accurate identification of the SLN and verification of its removal[55]. Further work by the same group combined the use of a γ probe with vital blue dye in a larger group of patients[54] and in this study all the nodes that were stained blue were also radiolabelled with the colloid. Further studies have confirmed that the combination of preoperative lymphoscintigraphy and intraoperative use of the γ probe can identify the SLN[52,53].

The sentinel node in breast cancer

The initial experience of intraoperative lymphatic mapping was largely in patients with melanoma. However, the technique has also been applied successfully in breast cancer. The first reported study used blue dye for mapping[59]. It contained 174 patients and used isosulphan blue to identify a sentinel node or nodes in 114 (66 per cent). The existence of a learning curve for sentinel lymphadenectomy using the blue dye technique was confirmed, with results significantly better at the end of the series than at the start. The SLN correctly predicted the status of the remainder of axillary nodes in 96 per cent of cases. In the latter half of this study, the SLN predicted with 100 per cent accuracy the nodal status of the rest of the axilla; all false-negative nodes occurred in the first half of the study. The authors argue on the basis of these results that intraoperative lymphatic mapping using blue dye can accurately identify the SLN, and that biopsy of this node can predict the nodal status of the axilla.

Giuliano *et al.*[59] reported a false-negative rate of 4 per cent (five of 114 cases in which the SLN was found). However, only 42 of the patients in this study were node positive. The SLN can only be a false negative where there is metastatic disease in the axilla and so the false-negative rate should be reported as a percentage of node-positive patients. Thus, in Giuliano's study the false-negative rate was 12 per cent (five of 42 patients). The false-negative rate is expressed in this fashion throughout the remainder of this review. The same group has published results more recently based on greater experience of the technique[60]. In their last reported series of 100 patients, the rate of detection of the SLN using the isosulphan blue technique was 93 per cent, with a 100 per cent accurate rate of prediction of axillary nodal status.

Other studies have been performed using blue dye for lymphatic mapping in the axilla[61–64]. These series have had smaller patient numbers and the results have been variable. In the study by Nieweg *et al.*[61], in which patent blue-V dye was used, 24 SLNs were identified in 27 patients. In all cases, the SLN accurately predicted axillary nodal status. A recent series has also been reported by Folscher *et al.*[62]. In these patients the dye used was methylene blue rather than patent blue-V. In all, 79 patients underwent surgery for breast cancer and a SLN was identified at operation in 32 (41 per cent). In a further eight patients (10 per cent) a SLN was found at the time of histological analysis of the resected specimen. Thus in 50 per cent of patients, no SLN was found. The false-negative rate in this series was 12 per cent. Feline work has shown that methylene blue is taken up poorly by the lymphatics resulting in poor staining of the lymph nodes[49], and this may account for the poor results in this study. In a more recent study using patent blue-V, the SLN was found in 82 per cent of 68 patients[63]; the false-negative rate in this series was 17 per cent (three patients). Horgan *et al.*[64] injected isosulphan blue around the tumour in 38 patients; a SLN was identified in 35, with three false negatives in 19 positive axillae. The results of intraoperative lymphatic mapping using vital blue dyes are promising. However, for this technique to become widely accepted in the management of breast cancer, it needs to identify the SLN reliably.

Lymphatic mapping with radionuclide may be used to increase the rate of identification of an axillary SLN in breast cancer[65–70]. Indeed lymphoscintigraphy for a multiplicity of purposes is well documented in this disease[71–76]. In one study, lymphoscintigraphy using technetium-99m-labelled antimony sulphide colloid injected around the tumour allowed the identification of a SLN in the ipsilateral axilla in 29 of the 34 cases examined[77]. Dynamic images were obtained immediately after injection of the tracer and static images were taken 2·5 h later. The authors commented that this allows the surface marking of SLNs. They suggest that the use of preoperative lymphoscintigraphy combined with intraoperative mapping using either blue dye or a γ probe should make sentinel node identification easier.

Several studies have examined preoperative lymphoscintigraphy with the intraoperative use of a γ probe. The largest of these is from Veronesi *et al.*[67] in Milan. A subdermal injection above the tumour site of 5–10 MBq technetium-99m-labelled human serum albumin was given to 163 patients the day before surgery. Scintigraphic images of the breast and axilla were taken at 10 min, 30 min and 3 h, and the skin was marked over the first lymph node that became radioactive. The hand-held γ

probe was used at operation to allow location of the SLN. A sentinel node or nodes were found in 98 per cent of patients and in 98 per cent of instances this node accurately predicted the status of the remainder of the axilla. It is of note that of the four patients with a false-negative SLN, the primary tumour was multifocal in two. The authors also commented that the method's predictive value in patients with tumours less than 1·5cm in diameter was 100 per cent.

There have been several other studies using lymphoscintigraphy and a γ probe[68–70,78]. Gill *et al.*[68] used preoperative injection of technetium-99m-labelled antimony sulphate. Lymphoscintigraphy and use of the γ probe identified a SLN in 30 of 36 patients. In 93 per cent of cases, the SLN correctly predicted the presence or absence of axillary metastases, with a false-negative rate of 8 per cent, although the number of node-positive patients is not reported. A study by Pijpers *et al.*[78] comprised 37 patients who had 40 MBq technetium-99m-labelled colloidal albumin injected around the tumour. Delayed imaging was performed at 2 and 18 h. A SLN was identified before operation in 34 patients and confirmed using the γ probe. In this study there were no false-negative nodes.

Roumen *et al.*[70] performed a larger study in the Netherlands. Eighty-three patients underwent injection of 60 MBq technetium-99m-labelled colloidal albumin. Images were obtained at either 4 or 18 h following injection, depending on the proposed timing of surgery, and a γ probe was used during operation to locate the SLN. This was identified in 57 patients (69 per cent), and there was one false-negative SLN in 23 positive axillae. Finally, Borgstein *et al.*[69] performed lymphoscintigraphy on 130 patients using an injection of 40 MBq of the same tracer. Images were obtained 2 and 18 h later, revealing focal axillary accumulations in 116 patients (89 per cent). Using a γ probe, 122 SLNs were found at surgery (94 per cent), although only 104 patients went on to formal axillary clearance. There was one false-negative sentinel node in 44 positive axillae.

The intraoperative use of a γ probe alone, without preoperative lymphoscintigraphy, has also been described[66]. The study was based on previous work by the authors in patients with melanoma, where use of a γ probe allowed successful identification of SLNs[54]. In a series of 22 patients, 0·4 mCi technetium-99m-labelled sulphur colloid was injected around the tumour between 1 and 9 h before operation. At surgery, a hand-held γ probe was used to identify the SLN, and a node was found in 18 of the 22 patients. This accurately predicted axillary status in all patients and there were no false negatives. A further study has been performed using technetium-99m-labelled dextran[79]. A dose of 1 mCi radiolabelled dextran was injected into the breast tumour or the site of excision biopsy in 41 patients. Using a γ probe, a SLN was identified in 40 cases, with no false negatives.

Some workers have combined the use of vital blue dyes with radionuclide techniques[65,80–82]. The largest of these studies, by Albertini *et al.*[65], describes the combination of a γ probe and isosulphan blue dye in 62 patients. Some 2–4 h before operation, 16 MBq technetium-99m-labelled sulphur colloid was injected around the tumour. After induction of anaesthesia, blue dye was injected at the same site. The sentinel node was then dissected out, guided by both the blue-stained lymphatics and the γ probe. A SLN or SLNs were identified in 92 per cent of cases; there were no false-negative sentinel nodes. The authors argue that the use of radiocolloid increased the success rate of identification from 73 to 92 per cent; that is, in 19 per cent of patients no blue dye appeared in the axilla, but the use of the γ probe allowed a SLN to be identified.

O'Hea *et al.*[81] have published a series of 59 patients from the Memorial Sloan-Kettering Cancer Center in New York. A SLN was identified in 75 per cent of patients using lymphoscintigraphy, 75 per cent using isosulphan blue and 88 per cent using the C-Trak γ probe (C-Trak Systems; Care-Wise, Morgan Hill, California, USA). A combination of isosulphan blue and the γ probe allowed SLN identification in 93 per cent of cases. Lymphoscintigraphy was performed 2–4 h before operation, with an injection of 0·3 mCi technetium-99m-labelled sulphur colloid. Images were obtained 50–60 min later. The true false-negative rate overall in this study was three of 20 node-positive patients. It is notable, in T_{1a} and T_{1b} tumours, that the SLN was identified in all cases, with no false negatives. The rate of successful SLN biopsy fell and the false-negative rate increased as tumour size increased.

Cox *et al.*[82] have published the largest series of SLN biopsies to date. Using a combination of isosulphan blue and a γ probe, a SLN was successfully identified in 440 (94 per cent) of 466 patients. Both injections were around the tumour, and 450 μCi technetium-99m-labelled sulphur colloid was injected between 1 and 6 h before operation. The authors examined both methods of lymphatic mapping individually, noting that a SLN was detected with isosulphan blue in 60 per cent of cases, and with radiocolloid in 68 per cent of cases. They concluded that the use of the two techniques in combination yielded greater success in lymphatic mapping. There were 105 node-positive patients in this series, and one false-negative SLN (1 per cent).

Table 1 summarizes the salient points of work published to date on the sentinel node in breast cancer.

The sentinel node and axillary staging

It seems clear from these studies that the concept of the SLN is valid, and supportive histopathological evidence has recently been produced[83]. This work confirms that the SLN is the axillary node most likely to contain metastasis. If it is tumour free using both haematoxylin and eosin staining and immunohistochemistry, the probability of non-sentinel node involvement is less than 0·1 per cent. This tends to suggest that axillary nodal metastasis in breast cancer occurs in the same orderly fashion as nodal metastasis in melanoma, that is according to the lymphatic anatomical drainage as proposed by Reintgen *et al.*[51]. So what has previously been described as 'skip metastasis' may be a consequence of variations in local lymphatic anatomy rather than a non-sequential spread of tumour cells. The incidence of skip metastases in several studies ranges from 1 to 42 per cent[19,40,84–89]. The variation in reported incidence of skip metastases may be due to differing techniques of axillary dissection, individual anatomical variations, or possibly failure to identify micrometastases in lower-level nodes. Where lymphatic mapping has been performed, the SLN has been found in level II in 18 per cent of cases by Roumen *et al.*[70], and in 23 per cent of cases by Giuliano *et al.*[59]. Allowing for the above variables, this would be roughly in keeping with the quoted figures for skip metastases. The conventional

Table 1 Sentinel lymph node biopsy studies in breast cancer

Reference	Year	Technique	No. of patients	Detection rate (%)	False-negative rate (%)	Prediction of axillary status (%)	Node-positive patients (%)
Giuliano *et al.*[59]	1994	Blue dye	174	66	12	96	36
Nieweg *et al.*[61]	1996	Blue dye	27	89	0	100	42
Folscher *et al.*[62]	1997	Blue dye	79	40	12	85	51
Flett *et al.*[63]	1998	Blue dye	68	82	17	95	31
Horgan *et al.*[64]	1998	Blue dye	38	92	16	84	50
Krag *et al.*[66]	1993	γ probe	22	82	0	100	39
Offodile *et al.*[79]	1998	γ probe	41	98	0	100	45
Veronesi *et al.*[67]	1997	Scintigraphy + γ probe	163	98	5	98	53
Pijpers *et al.*[78]	1997	Scintigraphy + γ probe	37	92	0	100	34
Borgstein *et al.*[69]	1998	Scintigraphy + γ probe	130	94	2	98	42
Roumen *et al.*[70]	1997	Scintigraphy + γ probe	83	69	4	96	40
Albertini *et al.*[65]	1996	Scintigraphy + blue dye	62	92	0	100	32
Cox *et al.*[82]	1998	γ probe + blue dye	466	94	1	100	23
O'Hea *et al.*[81]	1998	Scintigraphy + γ probe + blue dye	59	93	15	95	36
Gill *et al.*[68]	1997	Scintigraphy + γ probe + blue dye	36	83	8	93	—
de Vries *et al.*[80]	1997	Scintigraphy + γ probe + blue dye	10	100	0	100	60
Borgstein[121]	1997	Scintigraphy + γ probe + dye	33	100	0	100	56

division of axillary nodes into three levels is, however, based on anatomical landmarks rather than on the functional evidence provided by studies of lymphatic mapping, and perhaps this convention should be reconsidered.

There seems little doubt that the use of histological techniques in addition to the staining of a single section of lymph node with haematoxylin and eosin will improve the rate of detection of lymph node metastases. It has been known for some time that serial sectioning of resected nodes and staining of these sections with haematoxylin and eosin allows additional occult metastases to be detected[90–95]. The use of immunohistochemical techniques has also been demonstrated in several studies to increase the diagnostic yield of occult nodal metastases in patients who were classified as 'node negative' on standard histological examination[96–102]. In addition, there is evidence to suggest that the reverse transcriptase–polymerase chain reaction may be even more sensitive in the detection of occult disease[103–105].

More important, however, than the detection of such micrometastatic disease is to what extent, if any, it influences prognosis. This has been the subject of great debate. Initial studies suggested that micrometastases detected on serial sectioning did not have an adverse effect on prognosis[91,92,106,107]. However, more recently, larger studies have shown a reduction in both disease-free survival and overall survival in patients with micrometastases[93,94,99–102,108]. If patients with micrometastases are followed for 6 years, their survival is similar to that of node-negative patients[109]. However, at 10 years the survival rate of the former group is significantly poorer. The fact that a long follow-up period is necessary, together with the small patient populations in the early studies and the use of immunohistochemistry in more recent studies, almost certainly accounts for the differing results. A recent review article concludes that the use of conventional techniques will underestimate the presence of metastases in axillary lymph nodes, and that patients with micrometastases have a clear survival disadvantage[110].

Although the pathological methods detailed above allow more accurate nodal staging of the axilla, they are impractical in patients undergoing a standard axillary clearance. The majority of pathology departments do not have the resources to perform serial sections, immunohistochemistry and reverse transcriptase–polymerase chain reaction on all the nodes retrieved from an axillary clearance. SLN biopsy may allow more accurate staging of the axilla by allowing histopathological examination to concentrate on one or two nodes only. Recent work by Giuliano *et al.*[111] confirms this hypothesis. Evaluating the sentinel node using serial sections and immunohistochemistry, these authors found metastases in 42 per cent of patients, as opposed to 29 per cent when the specimen from a full axillary dissection was analysed in a routine fashion.

A detailed analysis of one or two sentinel nodes using serial sections and immunohistochemistry may offer an accurate, cheaper and simpler method of staging the axilla. The implication of this is, if a patient were to be truly node negative based on a thorough examination of the SLN, that no further axillary treatment would be necessary. This hypothesis will need to be validated by a randomized controlled trial with prolonged follow-up, comparing patients treated by SLN biopsy and no further treatment if the axilla is negative with patients treated by standard axillary dissection, taking axillary recurrence and overall survival as outcome measures.

Internal mammary lymph nodes

One further issue of note is internal mammary node metastasis. Metastases to the internal mammary nodes occur in around 20 per cent of patients with breast cancer[112,113]. In one study[113], the site of the tumour within the breast had no impact on the presence or otherwise of internal mammary node metastases. Another study from the same centre, however, suggested that internal mammary node involvement has a bearing on prognosis, with patients who had positive nodes in both the axilla and the internal mammary chain having the worst overall survival[114].

A multicentre prospective randomized clinical trial has shown that the addition of routine internal mammary node dissection to the procedure of radical mastectomy does not improve outcome[115]. Overall survival rates were very similar in both groups and the internal mammary recurrence rate was very low without dissection of the nodal chain. In light of this, Veronesi *et al.*[113] suggested, although there is no benefit to be gained from internal mammary dissection, that a biopsy of the internal mammary chain could be carried out via the second or third intercostal space. This would allow prognostic information regarding involvement of the chain to be obtained, while avoiding the morbidity of internal mammary dissection.

This may be relevant to SLN biopsy when it is performed with lymphoscintigraphy. Blue dye will not allow visualization of the internal mammary nodes, but when preoperative lymphoscintigraphic images are taken a sentinel node may be visualized in the internal mammary chain. Indeed, this has been described in studies on sentinel lymphadenectomy[70,77,78]. In one study involving 37 patients, drainage to the ipsilateral internal mammary chain was noted in five patients, in one of whom no axillary nodes were visualized[78]. In a further study, nine of 34 patients had a sentinel node in the internal mammary chain[77]. Finally, Roumen *et al.*[70] identified internal mammary SLNs in two of 83 patients. However, in none of these reports were the internal mammary nodes removed at operation and so the presence or absence of metastases in the chain could not be documented. It may be difficult to detect internal mammary nodes lymphoscintigraphically owing to the 'hot spot' from the tumour obscuring any 'hot' internal mammary nodes. Although it may be simple to pinpoint the surface marking of internal mammary nodes, they may not be visible in the lateral view as the primary tumour can obscure them making it difficult to measure the depth of these nodes[77].

Discussion

The work published to date on SLN biopsy in breast cancer confirms the validity of this concept. However, a clear surgical definition of what constitutes a sentinel node has not yet been established. Giuliano *et al.*[59] define a SLN as being the blue-stained node closest to the tail of the breast, or else the node at the termination of a blue-stained lymphatic even when that node is not blue[116]. This is an acceptable working definition where mapping is carried out using vital blue dye. The issue of a 'hot' sentinel node has been examined only by Cox *et al.*[82], who defined a 'hot' SLN as one where, *ex vivo*, the ratio of counts per second in the SLN was ten times that of a non-SLN. As the use of lymphoscintigraphy and γ probes becomes more common, it is important that this issue is examined and a reproducible distinction of the SLN from background noise, such as that used by Cox *et al.*, is established.

There has been little, if any, consensus on materials and methods in the published work on SLN biopsy. As discussed above, several different vital dyes have been used for lymphatic mapping. Both isosulphan and patent blue-V appear to yield good results; Morton *et al.*[48] suggested in their original description in melanoma that patent blue-V provided best visualization of the lymphatics.

The radiopharmaceutical used for lymphoscintigraphy may also affect the results. It is known that the biokinetics involved depend on particle size[117]. Where large particle colloids such as technetium-99m-labelled sulphur colloid are used (mean particle size 200 nm), absorption may be slow and consequently SLN visualization may be delayed or missed[66]. Small particle colloids, such as technetium-99m-labelled antimony sulphate (size 3–12 nm), may move rapidly through the lymphatics, with the consequence that non-sentinel nodes may be sampled mistakenly[77]. Technetium-99m-labelled colloidal albumin has been used by several authors[67,69,70,78] and 95 per cent of particles in this tracer are less than 80 nm in diameter. These studies suggest that this colloid is rapidly absorbed and transported by the lymphatics, with prolonged sequestration in the SLN and minimal overspill to higher-echelon nodes. Offodile *et al.*[79] do not discuss the rationale for using technetium-labelled dextran in their study. It has previously been suggested to be more accurate for lymphoscintigraphy than colloidal tracers, such as sulphur or albumin colloids, as it is removed from the injection site by lymphatics only, and migrates to the nodal basin more rapidly than other colloids[118]. However, little has been reported of its use in SLN biopsy in breast cancer.

There has been some debate about the optimal timing of imaging. In melanoma, dynamic lymphoscintigraphy has been advocated on the grounds that it will allow differentiation between overspill from the SLN and multiple SLNs[53]. Taylor *et al.*[119] stated in a series of 16 patients with melanoma that failure to obtain dynamic imaging may result in misdiagnosis of the SLN in a small percentage of cases, as static images do not define the pattern of lymphatic flow. However, it has been argued that, given the slower uptake and transport of tracer following injection in the breast, dynamic lymphoscintigraphy is impractical and unhelpful[70,78]. The study by Uren *et al.*[77] supports this, as dynamic imaging following injection showed uptake by lymphatic channels in only seven of 34 patients. The optimum timing for obtaining static images is also unclear. Borgstein *et al.*[69] suggest that nodal uptake will not be apparent for 2 h following injection of tracer, and Roumen *et al.*[70] state that the optimum timing in their experience is about 6 h. The importance of later imaging is supported by other studies, which showed that a significant number of patients had no axillary uptake at 2·0–2·5 h[77,78].

Several methods of injection have been described. Most workers use injection of radiolabelled tracer around the tumour and, as has been discussed, the consequence of this is delayed lymphatic uptake and the need for later imaging of the axilla. Nieweg *et al.*[61] injected directly into the breast tumour. It is not known whether any adverse effects accompany this. Veronesi *et al.*[67] used a technique of subdermal injection of isotope overlying the breast tumour, with a SLN detection rate of 98 per cent. This raises the question of whether the overlying skin shares its lymphatic drainage with the tumour. There is evidence that the lymphatics of the breast communicate with the subdermal plexus of the skin[120]. Borgstein *et al.*[121] have demonstrated complete concordance between the SLN of a breast tumour and its overlying skin in 33 patients, using intradermal patent blue-V and technetium-99m-labelled colloidal albumin injected around the lesion. The use of subdermal tracer allowed Veronesi *et al.*[67] to obtain scintigraphic images much earlier than in patients in whom injection around the tumour was employed, at 10 min, 30 min and 3 h. The success of early imaging in this study is in keeping with findings reported in melanoma, where intradermal injection of tracer followed by dynamic scintigraphy identified 95 per cent of SLNs within 20 min[53]. In summary, it appears that either injection around the tumour with delayed imaging or subdermal injection with dynamic and early static imaging are both potentially useful methods.

A further problem described in SLN radiolocalization is that of 'shine-through' from the primary tumour[70]. This is a particular problem with laterally located breast tumours, where the signal from the injected radiocolloid at the tumour site may obscure a 'hot spot' in the axilla. Lead masking of the primary tumour site may also obscure any focal lymph node accumulation, and it has been suggested that the patient pull her breast medially to minimize this problem[70].

Several different types of hand-held γ probe have been used in the published series: the C-Trak system and the Neoprobe 1000 (Neoprobe, Dublin, Ohio, USA). The use of a different type of probe does not appear to influence the outcome in any of these studies. However, the probes manufactured more recently are smaller in diameter and have an angled tip, to allow easier access within the axilla. The new Navigator probe (Auto Suture, Ascot, UK) has a 14-mm head and a smaller 10-mm probe has also been produced which allows access between the ribs to the internal mammary chain should this be required. Snap-on collimators may be used to reduce background radiation and narrow the probe's field. The use of such a collimator has been described in two series[69,78], and may partly account for the high rates of SLN identification using the γ probe in these studies, 94 and 92 per cent respectively.

The majority of the SLN studies in breast cancer contain a few patients in whom a SLN is not identified. It has been suggested that obstruction of the lymphatics by tumour cells may result in rerouting of the lymphatic drainage, resulting in an alternative node being labelled as the SLN, and increasing the possibility of false negatives[69]. However, Roumen *et al.*[70] argued that this hypothesis accounted for only two of their 17 scan-negative patients. Tumour site may conceivably explain why some tumours do not appear to drain to an axillary SLN, although previous studies of the lymphatics of the breast have shown that over 90 per cent of mammary lymph drains to the axilla, regardless of the site of intramammary injection[122,123].

These factors may be relevant to the practical use of this technique; two possible strategies could be adopted. One option is to biopsy the SLN for frozen-section analysis and, if it is positive, perform axillary clearance. If frozen-section analysis is negative, no further axillary surgery is needed. The drawback of this method is that there is a real risk of false-negative frozen-section analysis. Veronesi *et al.*[67] reported a false-negative frozen-section rate of 24 per cent. This represents a significant number of patients who need to undergo further axillary treatment. Similarly, recent data presented by Dixon *et al.*[124] suggest that intraoperative frozen-section analysis of axillary nodes has a false-negative rate of 10 per cent. Such a high false-negative rate would limit the usefulness of this strategy in practice. A two-stage procedure could, therefore, be employed, with the primary tumour excised and the SLN biopsied at the time of surgery. Accurate axillary staging could be performed using paraffin sections (and immunohistochemistry and reverse transcriptase–polymerase chain reaction if considered necessary) of the SLN; patients with a positive axilla would then return for further surgery. The alternative to this is that the first procedure is SLN biopsy alone, without excision of the primary tumour. Once the axilla has been staged in this way, the patient returns for excision of the tumour, together with axillary clearance if indicated. If a two-stage procedure were to be pursued, careful selection of patients for SLN biopsy would be required, as it would be appropriate only in patients with a low risk of nodal involvement, thus resulting in a low rate of reoperation. This would principally encompass patients with small or impalpable tumours who have been shown to have a low risk of axillary nodal metastasis[125]. Furthermore, it seems that SLN biopsy is more successful and has a lower false-negative rate in smaller tumours[67,81]. Few authors have discussed specifically the use of SLN biopsy in impalpable lesions. It would be feasible to inject dye or radiocolloid at the time of radiological localization of the primary tumour. Indeed, this may prove to be one of the areas where SLN biopsy is of most value. Finally, in centres where axillary sampling rather than clearance is the preferred surgical procedure, the accuracy of SLN biopsy in staging the axilla will have to be compared with that of the sampling procedure.

There has been no direct comparison of the use of vital blue dye with radionuclide methods for lymphatic mapping in SLN biopsy. These latter techniques add considerable expense to mapping and render the procedure more complex. Veronesi[126] has argued that lymphoscintigraphy allows identification of the sentinel node in nearly 100 per cent of cases, that the procedure is rapid and that accurate preoperative localization of the SLN before surgery allows an appropriately placed short incision to allow retrieval of the SLN. It is likely on the basis of published evidence that a combination of radiocolloidal imaging and intraoperative mapping with blue dye offers the best results.

It is now possible to identify the SLN in the vast majority of patients with breast cancer. However, there remain many unanswered questions with respect to the optimal technique for doing this and the clinical applications; future work needs to be directed at comparing the methods discussed above. It also remains necessary to elucidate the frequency and significance of sentinel nodes in the internal mammary chain. Finally, for SLN biopsy to become a worthwhile and accepted part of breast cancer management, it will be necessary to demonstrate in randomized controlled trials that patients with a negative SLN do not require further treatment to the axilla, and that such management does not adversely affect both their disease-free and overall survival.

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Annales de Chirurgie

Digest

Dr Denis Castaing, Editor of *Annales de Chirurgie*, chooses the best from issues eight, nine and ten of 1997.

A reciprocal digest written by our European Editor, Mr Colin Johnson, is published in the French journal.

Gynaecology

Surgery is an important part of the therapy of ovarian cancer. Part of number 10 of *Annales de Chirurgie* was dedicated to this problem.

The first paper from Michel *et al.*[1] from Villejuif, France, reviews the role of surgery in the staging and treatment of malignant tumours. The authors write that, regardless of the stage, assessment must include peritoneal cytology, hysterectomy with bilateral adnexectomy, omentectomy, pelvic and lumboaortic lymphadenectomy, appendicectomy and multiple peritoneal biopsies. For stage I tumours, in young women desiring a subsequent pregnancy, preservation of the uterus and contralateral ovary can be proposed. For stages II, III and IV, the therapeutic strategy consists of primary complete surgery and systematic chemotherapy (six cycles). Radical surgery is essential in these cases, as the size of the residual tumour at the end of operation constitutes the major prognostic factor. To optimize the quality of tumour debulking, the maximum number of visible carcinomatous nodules must be resected with, if necessary, gastrointestinal resection. The value of second-look surgery, after six cycles of chemotherapy, is currently controversial: it is only indicated in the context of randomized trials. Borderline malignant ovarian tumours have a good prognosis regardless of their stage. Surgery can very often be conservative, particularly in young women. Adjuvant chemotherapy has been shown to be effective in these tumours. Many studies are under way to define the value of new cytostatic molecules and 'interval' surgery (intercalated between several courses of chemotherapy).

Dauplat *et al.*[2] from Clermont Ferrand, France reported the surgical indications for patients at an advanced stage of disease with a bulky tumour in the pelvis and upper abdomen. The volume of the residual tumour after operation appears to be one of the most important prognostic factors in all series[3] and the most common therapeutic strategy begins with a surgical operation that allows histological diagnosis, accurate staging and maximal debulking. Optimal debulking can be achieved in about 75–80 per cent of cases with an extensive omentectomy, lymphadenectomy and intestinal resection. Patients whose tumour is completely or optimally debulked have a survival rate of about 50 per cent at 5 years. Moreover, it was demonstrated that the initial tumour bulk remains a poor prognostic factor even after debulking; the greater the tumour bulk the more aggressive must be the surgical procedure in order to be optimal and the final benefit will nevertheless be proportionally lower with a higher morbidity rate. The authors conclude that this paradigm indicates the need to assess accurately the initial tumour bulk in order to determine whether the tumour will be optimally debulked by means of a well standardized operation. If not, the alternative strategy would be three courses of chemotherapy as front-line treatment before debulking surgery, which hopefully would be made easier.

De Gramont *et al.*[4], from Paris, France, reported a study of women with advanced ovarian cancer treated by chemotherapy and then debulking surgery after an initial laparotomy. The therapeutic programme was cytoreduction laparotomy, IV cisplatin and anthracycline chemotherapy, early debulking surgery after three cycles of chemotherapy in the presence of initial residual disease greater than 2 cm and intraperitoneal consolidation chemotherapy. Among 160 women with stage III or IV disease, 80 (50·0 per cent) had residual tumour of more than 2 cm in diameter after laparotomy, but early debulking surgery was possible in only 54 (68 per cent), Thirty-eight women (23·8 per cent) had no residual disease, 42 (26·3 per cent) a residual tumour of less than 1 cm and 39 (24·4 per cent) residual tumour of between 1 and 2 cm. The median survival of the 80 patients with initial residual disease over 2 cm was 23 months; that of the women with no macroscopic residual disease was 44 months. For the authors, early debulking surgery appears useful in advanced ovarian cancer with bulky residual disease.

Paediatric surgery

Issue number 8 of *Annales de Chirurgie* results from a collaboration with the Surgical Canadian Association. In this issue, to review the experience of a paediatric institution with thyroid surgery, Giraux *et al.*[5], from Montreal, Canada, did a retrospective chart review of all patients who underwent thyroid surgery between 1980 and 1995. Fifty patients, 32 girls and 18 boys, underwent thyroid surgery. Clinical presentation included a thyroid nodule (36 patients), a family history of multiple endocrine neoplasia syndrome with a positive pentagastrin stimulation test (ten), diffuse nodular goitre (three) and a neonatal cervical mass (one). Radiological investigation included ultrasonography in 58 per cent of cases and radionucleide imaging in 70 per cent. The mean age at surgery was 13·3 years and the delay between onset of symptoms and diagnosis was 13 months. Twenty-one patients had a lobectomy with or without isthmectomy, 19 had a total thyroidectomy and ten underwent subtotal thyroidectomy. Nine patients required a second operation to complete the surgical treatment; total or near-total thyroidectomy was performed when the final pathology showed a carcinoma. A well differentiated carcinoma was found in 52 per cent of the patients, a medullary carcinoma in 20 per cent and a benign lesion in 28 per cent of cases. Nine patients had local or distant metastases at the initial operation. Postoperative treatment consisted of suppressive hormonotherapy in all cases of cancer and radioactive iodine when recurrence occurred (in 24 per cent of patients) and when metastasis was present. Survival remained at 100 per cent. The authors' conclusion was that thyroid nodules should be investigated rapidly in children because of a high potential for malignancy and that with aggressive surgical treatment and postoperative ^{131}I for recurrent lesions and metastasis the prognosis remains excellent.

A retrospective study compared open appendectomy via a McBurney incision and laparoscopic appendicectomy for complicated appendicitis (abscess or peritonitis)[6]. Some 150 children, with a mean age of 8·5 years, were operated on between January 1990 and April 1996, 92 via a McBurney incision and 58 by a laparoscopic approach. Only children with complicated appendicitis and positive bacteriology of peritoneal fluid were included in this study. All children received parenteral antibiotics for a mean of 5·4 days. The mean operating time was significantly longer in the laparoscopic group (63 *versus* 43 min; $P < 0.0001$). The conversion rate in the laparoscopic group was 12 per cent. The mean hospital stay was 8·4 (range 3–29) days and was similar for the two groups. There was no significant difference in the complication rate in the two groups (intraperitoneal abscess: ten in the laparoscopic group *versus* eight in the open group; obstruction: two *versus* three). However, wound infections were more frequent in the open group: nine *versus* one ($P = 0.008$). Late postoperative complications occurred in three patients (obstruction, two; wound dehiscence, one) in the open group and none in the laparoscopic group (*P* not significant). The authors' conclusion was that laparoscopic appendicectomy is a safe procedure for complicated appendicitis in children, but the greatest short-term benefit is cosmetic. Long-term results need to be evaluated, particularly with regard to the long-term complication rate.

Laparoscopy

To evaluate the role of laparoscopic surgery in patients with colonic polyps, Le Picard *et al.*[7], from Charenton-le-Pont, France, report the results of a prospective study. From April 1994 to April 1996, 16 consecutive patients were included. After initial laparoscopy, the colonic lesion was located easily and rapidly by colonoscopy. Under laparoscopic control (laparo-assisted), a new snare colonoscopic polypectomy was possible in six cases. If polypectomy was not possible, a minilaparotomy was performed above the polyp and allowed polypectomy by extraperitoneal colotomy in nine patients. In one patient, the polyp was not found on colonoscopy. No colectomy was needed. The final histological examination showed two Dukes A carcinomas justifying secondary wide colectomy. Le Picard *et al.* concluded that laparo-assisted polypectomy is a safe and efficient procedure, allows complete excision of polyps and may avoid a colonic resection.

Collet *et al.*[8], from Pessac, France, reported their experience with laparoscopic fundoplication. Surgical indications were failure of medical therapy, early recurrence of symptoms after interruption of medical treatment in young patients or large hiatal hernia associated with symptoms of reflux and/or symptoms of mediastinal compression. The type of the wrap was tailored according to the preoperative manometry: circumferential fundoplication in patients with normal oesophageal motility and partial wrap in patients with altered motility. Short gastric vessels were not divided routinely. From July 1991 to March 1997, 123 patients were operated on. Some 101 circumferential fundoplications were performed, 52 with division of short gastric vessels and 49 without, and there were 22 partial wraps. In four cases it was necessary to switch to open surgery (conversion rate 3·2 per cent) because of two enlarged left liver lobes, one oesophageal tear and one splenic injury. Six postoperative complications were observed (4·8 per cent), one of which was severe and led to the patient's death from necrosis of the fundus. After a mean(s.d.) follow-up of 1·7(1·4) years, four patients have transient recurrent reflux, and three patients have had annoying dysphagia requiring balloon dilatation in one case and reoperation in two cases. Four patients experienced late thoracic migration, in one case after a violent physical effort, requiring urgent reoperation; in the other three, the migration remained asymptomatic. The pH and manometric study performed in 41 consecutive patients before and after operation allows objective evaluation of the results.

Digestive surgery

In a retrospective series of 95 patients requiring emergency surgery for distal colonic obstruction, reported by Gramegna *et al.*[9], from San Remo, Italy, primary bowel resection followed by immediate anastomosis after intraoperative colonic irrigation was performed. Colonic carcinoma was the cause of obstruction in 81 cases (85 per cent); 13 patients had diverticulitis and one had sigmoid volvulus. The technique of on-table lavage was similar to that described by Dudley and colleagues[10] in 1980. A caecostomy tube was used in 86 patients (90 per cent) and was removed on the tenth postoperative day. Four patients died, none from complications of anastomotic leakage. There were three anastomotic leaks (3 per cent) and ten radiological leaks were observed. Three patients required reoperation. The mean hospital stay was 23 (range 13–50) days. The results of this study suggest that intraoperative colonic irrigation is effective, enabling the surgeon to perform primary anastomosis with reasonable safety after emergency resection of selected distal colonic lesions.

To assess the diagnostic accuracy of endoscopic ultrasonography for local and regional staging of oesophageal cancer, a prospective study was carried out between January 1992 and December 1995 by Giacoia *et al.*[11], from Marseille, France. Eighty-five consecutive patients, 28 of whom received previous induction therapy, were evaluated by endoscopic ultrasonography and operated on. Endoscopic ultrasonography was performed by a single physician who was not informed about the results of previous morphological explorations. Histopathological analysis of operative specimens was performed by the same pathologist, who was unaware of the results of endoscopic ultrasonography. Data were collected by another independent observer. Endoscopic ultrasonography resulted in incomplete staging in eight patients (9 per cent) with severe stenosis precluding endoscope passage. The accuracy, specificity and sensitivity of endoscopic ultrasonography in detecting the depth of oesophageal involvement were 82, 78 and 86 per cent respectively, and 72, 70 and 73 per cent respectively for lymph node metastasis. The overall accuracy of endoscopic ultrasonography in identifying the preoperative stage was 67 per cent, with a clear-cut alteration when patients had received induction therapy (61 *versus* 72 per cent). On the other hand, seven of the 11 patients thought to have a complete response at endoscopic ultrasonography had no residual tumour. The authors' conclusion was that endoscopic ultrasonography provides precise information for the preoperative identification of locally advanced oesophageal tumour, even after induction therapy.

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Association of Surgeons of Great Britain and Ireland

The Annual Scientific Meeting of the Association of Surgeons of Great Britain and Ireland was held in Edinburgh on 13–15 May 1998 under the Presidency of Mr A. E. B. Giddings. The abstracts of the oral and poster presentations of the original work presented at the meeting have been published in a BJS Supplement that accompanied the June 1998 issue of the Journal. The articles that follow in the present issue describe work presented at the Edinburgh meeting that have been accepted for publication after peer review by the Journal's referees. Other papers from this meeting will appear in subsequent issues.

John Murie
Joint Editor

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Subparietal hepaticojejunal access loop for the long-term management of intrahepatic stones

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Background The subparietal hepaticojejunal biliary access loop is a recognized technique for the long-term management of primary intrahepatic stone disease. This paper assesses the results of this approach in a series of South African patients.

Methods Between 1985 and 1997, 21 patients, of mean age 34 (range 24–66) years, underwent surgical extraction of intrahepatic stones and formation of an hepaticojejunal access loop. The access loop was subsequently used for further stone removal and stricture dilatation. Patients were followed prospectively (median 47 months) and details of the number and type of procedures performed, stone clearance rates, morbidity and subsequent outcome were recorded.

Results The distribution of intrahepatic stones was left lobe in 13 of 21 patients, right lobe in one and bilateral in seven. Six patients underwent additional left lobectomy at the initial operation because of associated atrophy of the left lobe. Following operation, stone removal and/or stricture dilatation was performed on 97 occasions (median 4 (range 0–24) procedures per patient). Complete stone clearance was achieved in 17 of 21 patients with partial clearance in the remaining four. There were no major complications and no deaths associated with the procedures.

Conclusion The subparietal access loop permits long-term access to the intrahepatic ducts allowing removal of stones and dilatation of strictures with minimal patient discomfort and low morbidity.

Primary intrahepatic stone disease (IHSD) is common in South East Asia with the highest incidence in Taiwan (30 per cent of all patients with gallstone disease), Hong Kong and Southern China, followed by Japan, Korea and Singapore[1]. Parasitic infestation with *Clonorchis sinensis* or *Ascaris lumbricoides*, and *Escherichia coli* bacterial infection, have been implicated in the pathogenesis[2]. Outside of South East Asia regions of high prevalence have been reported in Kashmir[3,4], Columbia[5] and the Western Cape province of South Africa[6]. The common features in each of these areas are poverty, social deprivation and endemic *A. lumbricoides* infestation. In the Western Cape province the disease is most commonly seen in fertile women with a previous history of *Ascaris* infestation.

Primary intrahepatic stones are associated with strictures in up to 85 per cent of cases[7] and the natural history is characterized by progression with recurrent attacks of biliary sepsis. Surgical removal of stones with an extrahepatic drainage procedure has been the standard management but residual stones and stone recurrence occur frequently whatever the technique[8,9–11]. Because of the need for repeated biliary instrumentation, long-term access routes involving percutaneous transhepatic access tubes[12], or hepaticocutaneousjejunostomy (HCJ) to permit stone retrieval or stricture dilatation have been developed[13–15]. These provide good access to the biliary system but patients are left with the unpleasant side-effects of a biliary stoma[11,14]. Experience with a subparietal hepaticojejunal access loop[16], without a stoma, in the management of IHSD is presented.

Patients and methods

Twenty-one patients (ten men) with IHSD underwent surgery between 1985 and 1997, with creation of a hepaticojejunal access loop. Nine patients had a total of 13 previous biliary tract operations (open cholecystectomy, seven; laparoscopic

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cholecystectomy, one; common bile duct exploration and sphincterotomy, two; choledochojejunostomy, two; laparotomy for unexplained abdominal pain, one) The mean age at operation was 34 (range 24–66) years. All patients have been followed up prospectively for a median of 47 (interquartile range 32–60) months.

Surgical technique

A bilateral subcostal incision was used to provide exposure of the porta hepatis. The common hepatic duct was opened at the confluence into the left and right ducts, and stones were retrieved. Intraoperative choledochoscopy was performed to identify intrahepatic calculi which were removed. Occasionally stricture dilatation using a Gruntzig balloon was used in an effort to remove all stones. When atrophy or multiple cholangitic abscesses were present a lobectomy was performed.

A biliary–enteric anastomosis was performed using a side-to-side anastomosis between the hepatic duct confluence and a jejunal Roux-en-Y loop. If the left or right duct was narrowed, the hepatic duct incision was extended beyond the stricture to provide a wide anastomosis. A site 12-cm proximal to the end of the jejunal loop was selected for anastomosis to the hepatic duct, which was performed using a single layer of interrupted 3/0 Maxon (Davis and Geck, Gosport, UK)[17]. Two Ligaclips (Ethicon, Edinburgh, UK) were used to mark the anastomosis for later radiological identification[16]. The closed proximal limb was attached to the anterior abdominal wall using 3/0 polypropylene sutures to fix it in a subparietal position (*Fig. 1*)[16]. Further Ligaclips were used to mark the width of the jejunal loop by clipping the sutures holding the access loop in place (*Fig. 2*). An umbilical feeding tube was passed through the skin and abdominal wall into the access loop to permit postoperative cholangiography.

Radiological technique

If obstructive jaundice, biliary pain or ascending cholangitis developed subsequently, biliary access was gained using radiological screening. Antibiotic prophylaxis using intravenous ampicillin 1 g and gentamicin 160 mg (or cefuroxime 1 g) was given 30 min before the procedure. Local anaesthetic was injected at the puncture site and the afferent loop was identified fluoroscopically by determining the position of the 'Ligaclip runway'. The loop was entered percutaneously between the 'runway' clips using a 21-G fine-bore needle with intermittent contrast injections and a guidewire. A converting dilator allowed percutaneous introduction of larger guidewire catheter combinations directed by fluoroscopy into the jejunal lumen and a combination of Dormia baskets, angioplasty balloons and snare wires was used to fragment and extract calculi. Biliary stenoses were dilated using 4–8-mm standard angioplasty balloons. On completion, the ducts were flushed with saline. After clearing stones in larger ducts, cholangiography often revealed additional stones in upstream segmental or side ducts which required further procedures. Neuroleptic analgesia was used as needed (midazolam). Patients were admitted overnight for observation and two further doses of antibiotics were administered following the procedure.

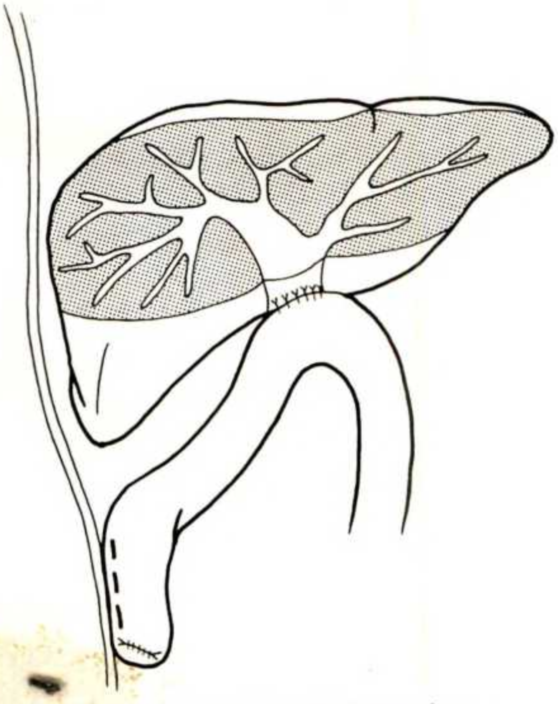
Fig. 1 Schematic diagram of subparietal access loop

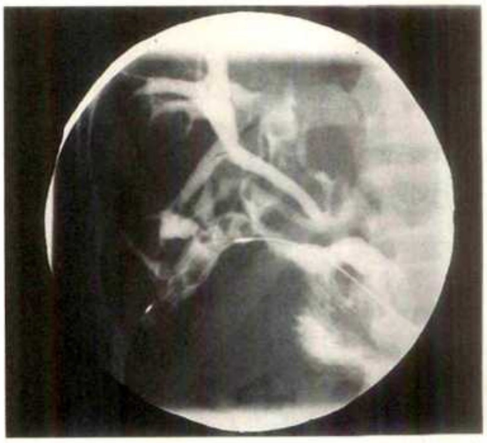
Fig. 2 Dormia basket extraction of stone via the access loop

Results

Distribution of intrahepatic stones

Stones were most commonly found in the left lobe of the liver; stones were confined to the left lobe in 13 of 21 patients, the right lobe in one and bilateral disease was present in seven. In patients with right lobe involvement, stones were seen predominantly in segments 6 and 7. Coexistent extrahepatic stones were found in four patients. Six patients had associated intrahepatic duct strictures although focal narrowings in dilated ducts were more common. Atrophy of segments 2 and 3 was identified before operation by computed tomography in six patients, all of whom underwent left lobectomy at the time of access loop formation.

Operative complications

Mean postoperative stay was 10 days. One patient who underwent left lobectomy developed a bile leak which settled without further intervention. There were two chest infections and one wound infection.

Use of the access loop

The subparietal access loop was used to gain access to the biliary tree in 19 of the 21 patients. A total of 97 procedures was attempted with successful access achieved in 95 (98 per cent). There was no significant complication of these procedures. The median number of procedures was 4 (range 0–24). Successful stone clearance was achieved in 17 patients with partial clearance in the remaining four. One patient, operated on early in the series, had an access loop length in excess of 12 cm which made radiological manipulation difficult because of loop redundancy. The remaining three patients had bilateral disease with multiple segmental duct involvement.

Discussion

Intrahepatic stones are frequently associated with intrahepatic strictures which may cause bile stasis, cholangitis and recurrent stone formation[18]. These may be true strictures or may be simply normal sized proximal ducts which are narrow compared with the dilated diseased distal duct[10]. Surgery is rarely curative and the natural history is one of progression with recurrent attacks of biliary sepsis[11]. The incidence of retained stones after operation is 48–77 per cent[8,18,19] and a number of strategies have been developed to enable removal of both retained and recurrent intrahepatic stones. After removal of as many of the intrahepatic stones as possible, reconstruction of the biliary tree by choledochoduodenostomy has not proved a reliable method for the management of subsequent intrahepatic stones[20,21]. Although direct endoscopic access is still possible, the presence of strictures, peripheral stone impaction and ductal angulation make endoscopic extraction difficult[22,23].

Roux-en-Y HCJ has been used in Asia to permit endoscopic access for the removal of intrahepatic stones[11,24,25]. This technique provides good access to the biliary tree and stone removal is successful in around 85 per cent of patients[26]. However, the necessity of a stoma is unsatisfactory because of the unpleasant side-effects of mucus and bile leakage with associated cutaneous irritation and excoriation, which is independent of afferent loop length[11,14]. Routine early closure of the stoma has been recommended to avoid these side-effects after removal of retained stones following surgery[27]. Stoma closure is associated with significant complications of persistent wound infection, fistula formation and parastomal hernia in 17 per cent[28]. Furthermore, 29 per cent of patients required reopening of the stoma for removal of recurrent stones after only 2 years of follow-up[28]. Closure of an access loop defeats its purpose since the natural history of IHSD is one of recurrences requiring further procedures, particularly when strictures remain.

An alternative access to the biliary tree for intervention is the percutaneous transhepatic approach although the standard radiological techniques are hampered by the extensive stone load present. The transhepatic route requires development of a working tract which necessitates sequential dilatation over a period of up to 3 weeks[29], following which choledochoscopy can be performed for stone removal or stricture dilatation. The procedure is not without complications, with severe pain (14 per cent) and bleeding (24 per cent) resulting in treatment failure in up to 22 per cent of cases[30]. Stone clearance rates of 80–83 per cent[31,32] have been achieved with repeated procedures. The transhepatic catheter has been a major source of patient complaint[11] and access is only temporary as the fistula closes after removal of the catheter[33]. This is particularly important since recurrent stones occurred in 33 per cent[32] and 40 per cent[31] of patients within 5 years following transhepatic choledochoscopy, requiring further transhepatic cannulation and tract formation.

The subparietal access loop used in this series has allowed reliable access to the biliary tree in 98 per cent of attempted cannulations. The stone clearance rate of 81 per cent (17 of 21 patients) is comparable to that of HCJ and transhepatic choledochoscopy. The median number of procedures performed per patient was 4 with one patient requiring 24 procedures over a 6-year period, emphasizing the need for a permanent access route. There was no complication attributable to the formation of the access loop and bacterial overgrowth of the Roux-en-Y loop[14] has not been observed. Segmental resection is appropriate when there is atrophy of segments 2 and 3 which occurs in around 20 per cent of patients[27]. Chronic inflammation may also be associated with the development of cholangiocarcinoma, reported in 2–9 per cent of patients with oriental IHSD[23,34,35], although none has occurred in the present series.

Percutaneous transhepatic choledochoscopy, choledochoscopy via HCJ, and interventional radiological procedures via a subparietal access loop each provide adequate stone removal and stricture dilatation in IHSD. The subparietal access loop offers the advantage of permanent access for stone removal with minimal discomfort and morbidity, without the additional morbidity of a biliary–cutaneous fistula or transhepatic access.

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Prospective evaluation of magnetic resonance cholangiography to detect common bile duct stones before laparoscopic cholecystectomy

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Background With the advent of laparoscopic cholecystectomy, endoscopic retrograde cholangiography (ERC) is frequently employed before operation to detect common bile duct stones. However, this is an invasive technique with recognized complications. This study evaluated the accuracy of magnetic resonance cholangiography (MRC) to detect choledocholithiasis in selected patients before laparoscopic cholecystectomy.

Methods Patients scheduled for elective laparoscopic cholecystectomy, with risk factors for common bile duct stones, underwent MRC followed by ERC or peroperative cholangiography.

Results Over a 2-year period 40 patients were studied. MRC had a sensitivity of 88 per cent, specificity of 93 per cent, positive predictive value of 78 per cent and negative predictive value of 97 per cent for the detection of common bile duct stones.

Conclusion MRC is a simple non-invasive method for preoperative screening for common bile duct stones in at-risk patients. In this study it would have reduced the need for ERC by three-quarters.

The approach to the detection of common bile duct (CBD) stones has altered with the introduction of laparoscopic cholecystectomy[1,2]. In the era of open surgery the majority of surgeons performed peroperative cholangiography with duct exploration if required. With the advent of minimally invasive techniques, peroperative cholangiography is performed less frequently[3]. This has resulted in increased use of endoscopic retrograde cholangiography (ERC) to detect and clear CBD stones before operation[4]. ERC is an invasive procedure with a well documented complication rate[5] and, despite restricting its use to patients with risk factors for CBD stones, up to one-third of patients may undergo ERC before laparoscopic cholecystectomy[6].

Magnetic resonance cholangiography (MRC) is a non-invasive technique that requires no contrast and allows detection of biliary pathology with a high degree of sensitivity and specificity[7]. The aim of this study was to compare prospectively the accuracy of MRC with ERC in the detection of CBD stones in patients with risk factors for choledocholithiasis.

Patients and methods

From February 1996 to January 1998 all patients scheduled for elective laparoscopic cholecystectomy with risk factors for choledocholithiasis (abnormal liver function test results, previous mild gallstone pancreatitis, dilated CBD of 7 mm or more, previous jaundice) underwent MRC. Patients with jaundice, cholangitis or severe acute gallstone pancreatitis were excluded and underwent early ERC. Patients having emergency laparoscopic cholecystectomy were also excluded.

MRC scans were performed on a 1·5-T Phillips scanner (Phillips Medical Systems, The Netherlands) using a T2-weighted Turbo Spin Echo sequence acquired with non-breath-holding in the coronal plane and interpreted by one radiologist. After MRC all patients underwent ERC within 1 week; the operator was unaware of the MRC result. Stones detected at ERC were cleared endoscopically. If ERC was unsuccessful, peroperative cholangiography was performed.

At the end of the study, MRC results were compared with ERC or peroperative cholangiography findings. Statistical analysis was by χ^2 test.

Results

Over the 2-year period 405 patients underwent laparoscopic cholecystectomy, of whom 278 had no risk factors for CBD stones. No patient from this group subsequently presented with symptomatic bile duct stones during the study period. Eighty-seven patients presented with jaundice, cholangitis or severe acute gallstone pancreatitis and underwent early ERC. Risk factors for CBD stones were present in 40 patients, who underwent MRC as part of the study. Two patients failed to complete MRC because of claustrophobia; they underwent ERC and one was found to have a bile duct stone. ERC was unsuccessful in four patients who subsequently had successful peroperative cholangiography.

MRC identified seven of eight patients found to have CBD stones in the study group (*Fig. 1*). Two patients were incorrectly diagnosed as having CBD stones by MRC. In the study group of 40 patients MRC had a sensitivity of 88 per cent, specificity of 93 per cent, positive predictive value of 78 per cent and negative predictive value of 97 per cent (*Table 1*). If ERC had been limited to patients with a positive or failed MRC its requirement would have been decreased from 40 to 11 patients ($\chi^2 = 0{\cdot}022$, 1 d.f., $P < 0{\cdot}001$).

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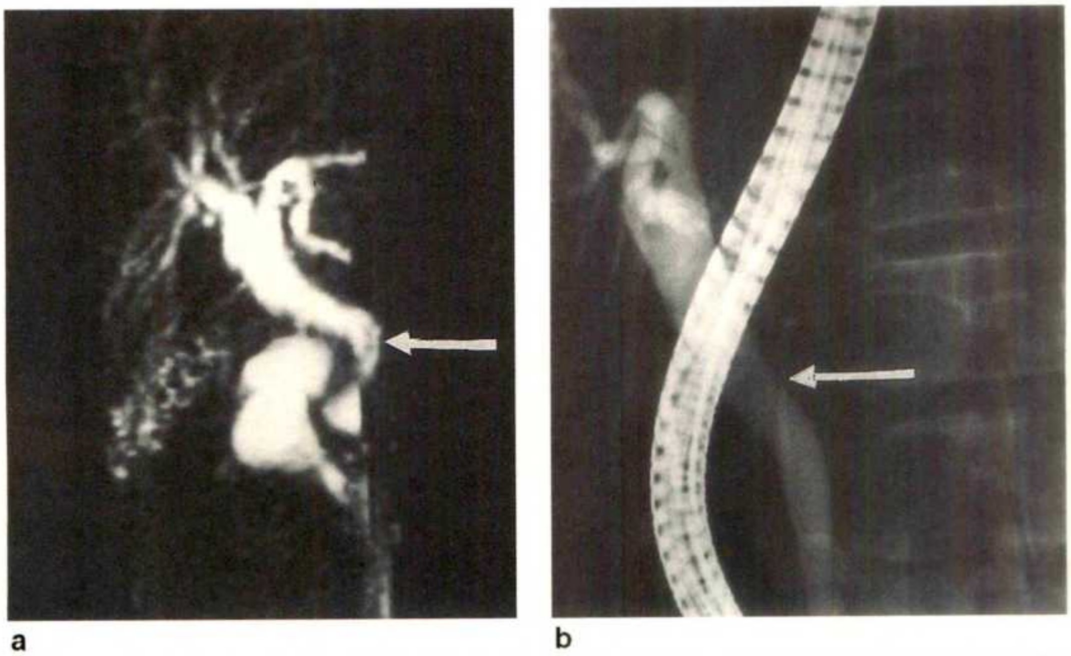

Fig. 1 a Magnetic resonance cholangiogram showing two small stones in the distal common bile duct (CBD) (arrow). b The corresponding endoscopic retrograde cholangiographic image

Table 1 Comparison of magnetic resonance cholangiography with endoscopic retrograde cholangiography or peroperative cholangiography for the detection of bile duct stones

	Endoscopic retrograde cholangiography or peroperative cholangiography	
	Positive	Negative
Magnetic resonance cholangiography		
Positive	7	2
Negative	1	28
Total	8	30

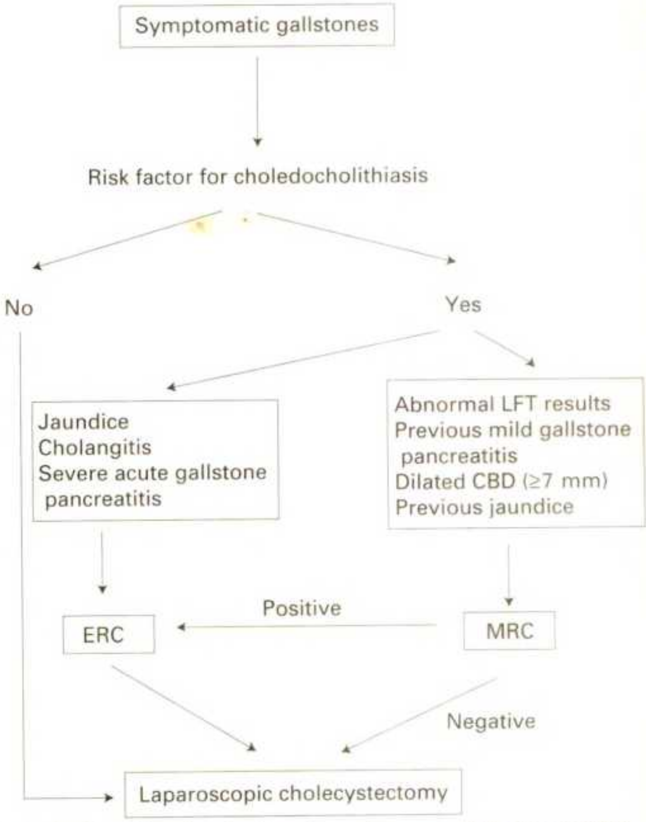
Symptomatic gallstones
Risk factor for choledocholithiasis
No
Yes
Jaundice
Cholangitis
Severe acute gallstone pancreatitis
Abnormal LFT results
Previous mild gallstone pancreatitis
Dilated CBD (≥7 mm)
Previous jaundice
ERC
Positive
MRC
Negative
Laparoscopic cholecystectomy

Fig. 2 Algorithm for the detection of common bile duct (CBD) stones before laparoscopic cholecystectomy. ERC, endoscopic retrograde cholangiography; LFT, liver function test; MRC, magnetic resonance cholangiography

Discussion

A selective policy of cholangiography in cholecystectomy has been shown previously to be safe in the era of open cholecystectomy[8]. For patients with risk factors for CBD stones, cholangiography was performed and, if stones were found, bile duct exploration and stone clearance were carried out. The introduction of laparoscopic cholecystectomy has led to decreased use of peroperative cholangiography[9], and laparoscopic bile duct exploration is limited to a few specialized centres[10]. Risk factors for choledocholithiasis are well recognized[11] and there is a move to identification of CBD stones before operation. ERC is currently accepted as the 'gold standard' for bile duct imaging and has the advantage of permitting the bile duct to be cleared of stones. However, it is an invasive technique with a reported mortality rate of up to 1 per cent, even in experienced hands[5]. Ideally its use should be restricted to therapeutic procedures alone.

Intravenous cholangiography has been shown to be sensitive and specific in the detection of CBD stones and has been advocated to reduce ERC rates before laparoscopic cholecystectomy[12]. However, it is an invasive technique and there remain concerns about safety despite the use of newer contrast media[13]. Endoscopic ultrasonography has also been demonstrated to be comparable to ERC in the detection of CBD stones[14,15]. However, this technique is also invasive, is not yet widely available and relies greatly on operator experience.

MRC is a non-invasive imaging technique that does not require the use of X-rays or contrast media[16]. It utilizes T2-weighted pulse sequences which provide a high degree of contrast between stationary fluids, such as bile, and solid organs and blood. It is performed on an outpatient basis without any special patient preparation. MRC has been shown to demonstrate normal and variant biliary anatomy accurately[16], as well as benign and malignant causes of bile duct obstruction[17]. Other studies have previously shown a sensitivity and specificity of 95–100 per cent in the detection of CBD stones[18–20]. However, these studies have not looked specifically at its use in the clinical scenario of patients before laparoscopic cholecystectomy. MRC is associated with a small failure rate, most commonly due to claustrophobia, but overall failure to obtain adequate images occurs half as frequently with MRC compared with ERC[16].

The present study demonstrates that, in patients with risk factors, MRC is an accurate imaging technique for the detection of CBD stones before laparoscopic cholecystectomy. Patients with jaundice, cholangitis or severe acute gallstone pancreatitis require early ERC but those with other established risk factors may undergo MRC (*Fig. 2*), leading to a significant reduction in preoperative ERC and its potential complications.

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Popliteal artery entrapment syndrome: collaborative experience of the Joint Vascular Research Group

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Background Popliteal artery entrapment syndrome (PAES) is rare and probably underdiagnosed. This study reviewed a collected experience.

Methods Patients were identified by the Joint Vascular Research Group (vascular surgeons from ten hospitals serving a population of approximately four million) during 1984–1995. Case notes were reviewed.

Results Twenty-one legs in 17 patients were identified with PAES. There were 15 men and two women. The median age at presentation was 29 (range 14–45) years. One patient was excluded because no further information was available. PAES was bilateral in four patients in whom three legs were asymptomatic. At presentation, the duration of symptoms ranged from a few hours (acute leg ischaemia) to intermittent claudication of 6 years' duration. Primary investigation included angiography (20 patients), duplex imaging (four), plain radiography (one) and magnetic resonance imaging (one). In two cases, attempted thrombolysis failed. Surgery was carried out on 17 legs but failed in two. No amputations were required. Following surgery, 12 legs were asymptomatic and five had residual symptoms.

Conclusion PAES should be excluded in young patients with intermittent claudication or acute ischaemia.

In 1879, T. P. Anderson Stuart, an Edinburgh medical student, described an anatomical variant of the popliteal artery dissected from a gangrenous limb[1]. The significance of this anomaly was not recognized until 1965, however, when Hamming and Vink from the Netherlands described the clinical syndrome caused by entrapment of the popliteal artery[2]. Since then, only a small number of series have been reported. Popliteal artery entrapment syndrome (PAES) is rare but it is important that it is recognized and treated expeditiously as it affects young people and is eminently curable.

This paper presents the collected experience of PAES by the members of the Joint Vascular Research Group (JVRG) from 1984 to 1995.

Patients and methods

The JVRG consists of vascular surgeons from ten hospitals in the UK serving a population of approximately four million people. Patients were identified retrospectively and their records retrieved. A pro forma was completed containing details about presentation, investigation, management and outcome.

Results

PAES was diagnosed in 21 legs of 17 patients. There were 15 men and two women. The median age at presentation was 29 (range 14–45) years. For one patient, no information apart from demographic details was available; the patient was excluded from further analysis.

PAES was bilateral in four patients; three limbs were asymptomatic. One patient presented with acute leg ischaemia and the remainder with intermittent claudication. The primary investigations included angiography (20 patients), duplex imaging (four), plain radiography (one) and magnetic resonance imaging (one).

Table 1 Surgical procedures performed for popliteal artery entrapment syndrome

Procedure	No.
PAR	4
PAR, thromboendarterectomy and vein patch	4
PAR and vein patch	2
Interposition graft	2
Femoropopliteal graft	4
Thromboendarterectomy and excision of bony exostoses	1

PAR, popliteal artery release

Two patients had initial thrombolysis which failed and went on to surgical reconstruction. A total of 17 legs required surgery (*Table 1*). Two patients have been reported previously[3,4]. There were two failed primary operative procedures, one femoropopliteal bypass and one interposition vein graft; both legs required further surgery which was successful. Following surgery, 12 legs were asymptomatic but five had residual claudication. No surgery was undertaken in three legs; in two the popliteal artery was occluded but the patients had only mild claudication, and in one the popliteal artery was patent and asymptomatic but the patient refused popliteal artery release. No legs required amputation.

Discussion

Patients with PAES typically present in early adult life. Hamming and Vink reported the first surgical case[2] but the condition is infrequently described in the literature and is probably underdiagnosed. Gibson *et al.*[5] described the anomaly in four limbs from three cadavers (3·5 per

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cent) of 86 autopsies. In a series of 20 000 Greek soldiers, Bouhoutsos and Daskalakis[6] found 45 affected legs in 33 symptomatic patients (incidence 0·17 per cent), leading them to conclude that PAES seldom causes symptoms. If PAES has been diagnosed in one limb, the contralateral limb should be screened as the condition is not infrequently bilateral[7–9]. The condition is more common in men, possibly because of their superior muscular development[10]; calf claudication in a young man should suggest popliteal entrapment[11]. Overtraining may produce a similar syndrome in athletes[12] and cramp after intensive physical training may be the dominant symptom[3].

Much of the recent literature focuses on the difficulty of making the diagnosis. In the present series angiography was the most frequently employed investigation. The use of duplex imaging for diagnosis and screening has recently been reported[13] but this gives an unacceptably high rate of false-positive results, particularly in athletes[14,15]. Computed tomography is of value in the diagnosis and management of PAES[16,17] but magnetic resonance imaging is increasingly recognized as having an important role in demonstrating the abnormal relationship between the heads of gastrocnemius muscle and the popliteal artery[8,18,19].

The management of a patient with PAES depends largely on the clinical picture. Surgery to release the entrapment and/or relieve the ischaemia following occlusion is the treatment of choice. Bypass can be carried out using the posterior approach with the patient prone. Good access is afforded to the artery and structures of the popliteal fossa, facilitating both confirmation of the diagnosis and popliteal artery release. Thromboendarterectomy and vein patching may seem an attractive option but appears to give inferior results compared with interposition vein grafting[11]. In this series no patient needed an amputation. Young patients have a particularly resilient collateral circulation.

There is concern that PAES is underdiagnosed. In the present study 21 affected limbs were identified in an estimated population of four million over 12 years. The incidence of PAES in other series was much higher[5,6]. Young or middle-aged patients may present with an occluded popliteal artery and subsequently undergo reconstruction to a distal vessel, or even amputation, without the underlying pathology being recognized.

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Lower limb surveillance following autologous vein bypass should be life long

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Background The aim of the study was to investigate whether infrainguinal vein graft surveillance can be stopped at 1 year without prejudicing graft or leg survival.

Methods Data were collected prospectively on 351 infrainguinal vein bypass grafts (326 patients) that had been entered into a vein graft surveillance programme between 1988 and 1997.

Results Some 104 grafts (30 per cent) developed significant new vein graft stenoses, 95 (91 per cent) of which occurred within 12 months. After 1 year, the risk of developing a significant graft stenosis was 3 per cent per year. Sixty-nine grafted limbs (20 per cent) developed new arterial inflow or run-off stenoses that required intervention, but only 37 (54 per cent) occurred within the first year, after which the risk was 9 per cent per year. The overall risk of developing a new vein graft or arterial stenosis after 1 year was 10 per cent per year.

Conclusion The incidence of vein graft stenosis decreases significantly 1 year after operation but there is still at risk of developing potentially graft-threatening arterial stenoses. Legs that have undergone infrainguinal vein bypass grafting should continue to be monitored in a surveillance programme for life.

Vein graft surveillance improves long-term infrainguinal vein graft patency by 15–26 per cent[1,2] and as a result many institutions have instigated surveillance programmes[3–6]. In this unit the vein graft, its anastomoses, and native inflow and outflow arteries are imaged with a colour-coded duplex scanner every 3 months for the first year and 6 monthly thereafter.

Intimal hyperplasia is the cause of vein graft stenosis occurring more than 1 month after operation[7,8]. The incidence of new vein graft stenoses decreases significantly after the first postoperative year[9] and this has prompted a suggestion that vein graft surveillance could then stop because the risk of developing a stenosis does not justify the cost of surveillance[10–13]. This study investigated the incidence of significant new vein graft and arterial stenosis in infrainguinal vein bypasses which had been inserted over 1 year previously.

Patients and methods

Between July 1988 and July 1997, 351 infrainguinal venous bypasses were performed on 326 patients. All patients were entered into a vein graft surveillance programme. Each postoperative visit to the vascular studies unit involved a clinical assessment, measurement of resting ankle:brachial pressure indices and duplex imaging of the grafted leg. Duplex imaging was performed at 1, 3, 6, 9 and 12 months after operation and at 6-month intervals thereafter. From 1991 a colour-coded duplex scanner (Diasonics Spectra; Diasonics Sonotron, Bedford, UK) was used to image the inflow vessels, the vein graft and run-off vessels.

A significant arterial stenosis requiring treatment was defined as that having a peak velocity ratio (PVR) of 2 or more[14]. Previously published data have shown that this ratio is the best predictor of an arterial stenosis of 50 per cent or greater. A significant vein graft stenosis requiring treatment was defined as that having a PVR of 3 or more[13]. A PVR of 3 or greater is the ratio at which there is a high risk that the stenosis will progress and threaten graft patency. Initial treatment of arterial and vein graft stenoses was by percutaneous transluminal angioplasty (PTA). Vein graft stenoses with a PVR of less than 3 were monitored more frequently depending on their severity. A new arterial or vein graft stenosis was defined as a newly identified stenosis occurring in an area of graft that was previously completely normal. The data were recorded on separate surveillance case notes and also entered on to a computer data spreadsheet. For the purpose of this study all new stenoses that developed both before more than 12 months after operation were identified from the database and reviewed.

Statistical analysis

Primary patency was defined as uninterrupted patency after the initial surgery with no other procedure performed on the graft. Primary assisted patency described a patent graft that may have remained patent as a result of secondary procedures, such as PTA. Secondary patency allows procedures to be performed that can salvage an occluded graft. Patients who died during follow-up were censored to their last attendance at the vascular studies unit. Kaplan–Meier cumulative patency curves, cumulative risk and life-table analysis were generated on SPSS (SPSS, Chicago, Illinois, USA) for the Power Macintosh and differences in primary, primary assisted and secondary patency rates were calculated with the log rank test. Statistical significance was accepted at $P < 0.05$.

Results

The median (range) age of patients undergoing infrainguinal vein bypass was 71 (19–97) years with a male to female ratio of 2:1 (217 men, 109 women). Patients' preoperative risk factors were similar to those reported

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Table 1 Site of distal anastomosis and conduit used for 351 infrainguinal vein grafts

Site of distal anastomosis	Conduit			
	ISVG	RVG	Composite	Total
Above-knee popliteal artery	12	19	0	31
Below-knee popliteal artery	49	53	5	107
Tibial vessels	114	74	25	213
Total	175	146	30	351

ISVG, *in situ* vein graft; RVG, reverse long saphenous vein graft; composite, combination of arm and leg vein

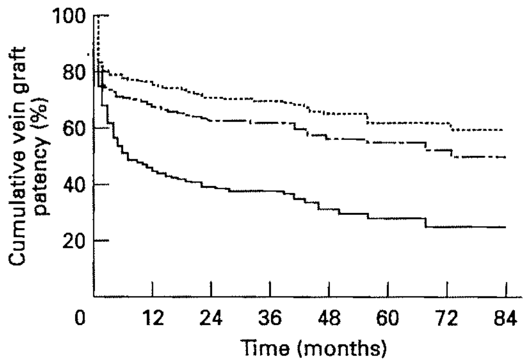
previously[15]; 122 patients (37 per cent) were hypertensive, 85 (26 per cent) had a previous history of ischaemic heart disease, 101 (31 per cent) had diabetes mellitus, 50 (15 per cent) had a history of stroke and 81 (25 per cent) continued to smoke after operation. Two hundred and seventy vein grafts (77 per cent) were performed for critical ischaemia, 54 (15 per cent) for severe claudication and 27 (8 per cent) for a popliteal aneurysm. The types of graft performed and conduits used are shown in *Table 1.*

The 30-day mortality rate was 9 per cent (30 patients) and the 1- and 5-year cumulative patient survival rates were 77 and 54 per cent respectively. Twenty-three (7 per cent) of the vein grafts failed within the first 24 h and 62 (18 per cent) of the grafts had failed by 30 days. Of 351 grafts 118 (34 per cent) occluded at some point during the study. Twenty-one of these occlusions occurred after at least 12 months of surveillance, at a median (range) of 22 (12–87) months after operation. Of these 21 vein grafts, ten previously had significant vein graft stenoses treated within the first year of surveillance, two previously had significant vein graft stenoses treated after 12 months of surveillance and nine had never had a stenosis identified. At 6 weeks after operation 100 patients/operated legs were not entered into the postoperative vein graft surveillance programme because 36 patients had died, 53 grafts had occluded (nine patients who had an occluded graft also died), four legs required major amputation despite a patent graft and seven patients were lost to follow-up.

The median (range) duration of postoperative vein graft surveillance was 25 (1–107) months. At 1 year the primary, primary assisted and secondary patency rates were 44, 67 and 76 per cent respectively and at 5 years the respective rates were 27, 55 and 62 per cent (*Fig. 1*). The 1- and 5-year cumulative limb salvage rates were 81 and 74 per cent respectively.

Vein graft and arterial stenoses

One or more significant vein graft stenoses required radiological or surgical intervention in 104 vein grafts (30 per cent). Overall 14 stenoses (11 per cent) were at the proximal anastomosis, 19 (14 per cent) in the upper third of the vein graft, 26 (19 per cent) in the middle third, 34 (26 per cent) in the lower third and 40 (30 per cent) at the distal anastomosis. PTA was the initial treatment for all stenoses; however, this was unsuccessful in seven vein grafts and these required immediate surgical intervention (three vein patch angioplasties and four autologous vein jump grafts). The cumulative development of 133 new stenotic lesions is shown in *Fig. 2*. The majority of stenoses occurred within the first 6 months after operation. Of the 104 failing grafts, 95 (91 per cent) required intervention within 12 months of operation. Of the new vein graft stenoses that occurred in nine vein grafts after more than 12 months, seven were at the distal anastomosis, of which six were associated with run-off stenoses close to the site of anastomosis. The other two stenoses were at the proximal anastomosis and the lower third of the graft.



No. at risk

Primary patency	351	107	67	44	24	13	7	3
Primary assisted	351	166	109	76	46	32	21	10
Secondary	351	189	130	90	58	41	27	15

Fig. 1 Primary (———), primary assisted (— - — -—) and secondary (-----) patency rates for 351 vein grafts. $P < 0.00001$ (primary *versus* primary assisted); $P < 0.0001$ (primary assisted *versus* secondary) (Mantel–Haenszel test)

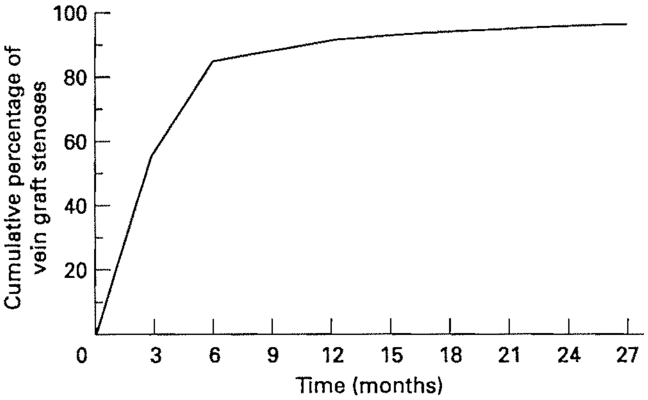


Fig. 2 Cumulative development of 133 new vein graft stenoses occurring in 351 infrainguinal vein grafts

After treatment of these new stenoses, 58 of 104 vein grafts went on to develop a further graft-threatening recurrent or new stenosis that required intervention at a median (range) time of 9 (1–73) months after the initial intervention. The cumulative risk for developing a new vein graft stenosis in a vein graft that had previously been stenosis free decreased after 12 months (*Fig. 3*). After 12 months of postoperative surveillance, the risk of developing a new vein graft stenosis was 3 per cent per year.

During the study 69 grafted legs were identified that had developed isolated significant native artery stenoses with a PVR of 2 or more. Thirty-seven (54 per cent) of

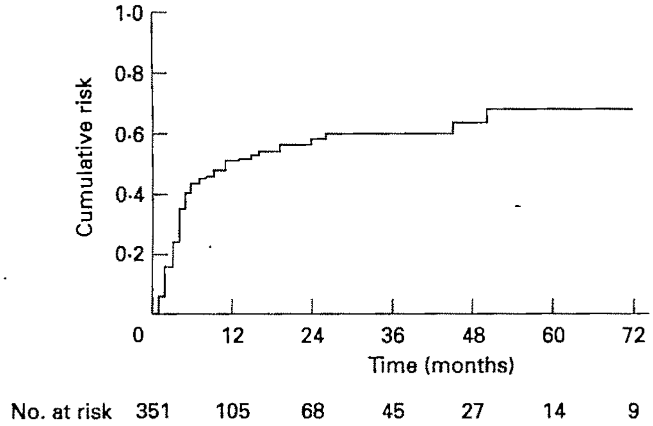


Fig. 3 Cumulative risk for the development of a significant new vein graft stenosis in 351 vein grafts ($n = 104$)

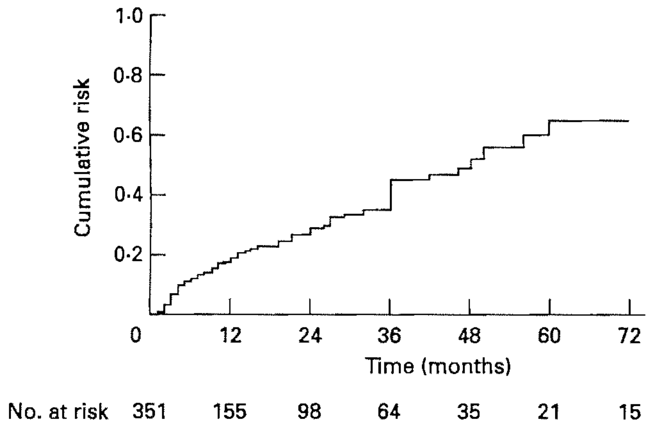


Fig. 4 Cumulative risk for the development of a significant new arterial stenosis in 351 infrainguinal vein grafts ($n = 69$)

the stenoses occurred within 12 months of surveillance. The risk of developing a significant arterial stenosis after 12 months in a leg that had previously been stenosis free was 9 per cent per year, and appeared to increase in a linear fashion (*Fig. 4*). After 12 months, 14 legs that had never previously had any vein graft or arterial stenosis subsequently developed a graft-threatening arterial stenosis. Six of these were associated with distal anastomotic vein graft stenoses. Of the 14 grafts, 11 had run-off stenoses, six of which were in grafts with single-vessel run-off.

During the study, 171 of 351 vein-grafted legs were in the surveillance programme for more than 12 months; only 78 could be identified that were completely free from vein graft stenoses and arterial stenoses. These 78 grafts are at a low risk of developing graft-threatening stenosis and thus vein graft surveillance could potentially cease after 12 months in these patients. However, although the risk of developing a new vein graft stenosis was only 3 per cent per year, the overall risk of developing a significant vein graft and/or arterial stenosis was 10 per cent per year. In this particular patient population 17 (22 per cent) of 78 legs that were stenosis free up to 12 months subsequently developed graft- and potentially limb-threatening vein and/or arterial stenoses.

There was no difference in the incidence of vein graft stenosis in grafts performed for severe claudication *versus* those for critical ischaemia ($P < 0{\cdot}1$); however, grafts performed for a popliteal aneurysm did have an overall lower incidence of vein graft stenosis ($P < 0{\cdot}04$) than those performed for occlusive disease. Only two of 27 grafts performed for popliteal aneurysm developed a run-off arterial stenosis compared with 67 (21 per cent) of 324 performed for occlusive disease ($P < 0{\cdot}001$). There was no difference in the incidence of arterial stenosis between grafts performed for critical ischaemia (54 (20 per cent) of 270) and those performed for severe claudication (13 (24 per cent) of 54) ($P < 0{\cdot}15$).

Discussion

Vein graft occlusions that occur within the first month after operation are a result of technical operative errors, whereas graft-threatening stenoses that occur after 1 month can be attributed to initimal hyperplasia[8,16]. Vein graft stenoses are said to occur in 20–30 per cent of infrainguinal vein grafts[12,17,18]; however, this figure is largely dependent on the sensitivity of the imaging method and the care of the search. In this series, 104 grafts (30 per cent) developed a stenosis severe enough to warrant intervention. By 6 weeks after operation 100 grafts were not eligible for the surveillance programme, leaving 251 grafts for follow-up. If these grafts alone are considered then the incidence of vein graft stenosis is relatively high (41 per cent). Most studies report a lower incidence calculated as a proportion of all grafts performed.

The incidence of intimal hyperplasia is maximal within the first 6 months after operation and then drops considerably after 12 months, after which it has been suggested that vein graft surveillance could stop. In the present study 91 per cent of all new vein graft stenoses occurred within the first year; thereafter the risk was 3 per cent per year. On the basis of these figures alone, vein graft surveillance could be stopped after 1 year. However, this figure does not take into account subsequent recurrent and new vein graft stenoses or the progression of native vessel atherosclerosis. A vein graft that develops a stenosis is at higher risk of developing subsequent recurrent or new lesions. Of the 104 grafts that required treatment of a graft-threatening vein graft stenosis, 58 (56 per cent) developed subsequent lesions a median of 9 months later. Grafts that develop a stenosis are subsequently 'at-risk grafts' and need to be monitored indefinitely. Apart from intimal hyperplasia, the other factor contributing to 'the failing graft' is native vessel atherosclerosis. In this study, the risk of developing an arterial stenosis was constant throughout the life of the graft with an average risk after 1 year of 9 per cent per year. The majority of vein graft stenoses that developed after 1 year were associated with an adjoining arterial stenotic lesion. When the risk of developing either new vein graft or arterial stenoses was combined, the yearly risk was 10 per cent.

In which vein grafts could surveillance be stopped, and when? Vein grafts performed for popliteal aneurysm have a low incidence of vein graft and arterial stenosis, but a high incidence of developing true vein graft aneurysms (12 of 27)[19,20]. Grafts that develop a stenosis are subsequently 'at risk'. Theoretically, surveillance of vein grafts that have reached 12 months without any graft-threatening event could be stopped. Only 78 of these were found in the present study and 17 (22 per cent) subsequently developed graft-threatening vein or arterial stenosis during follow-up, a yearly risk of 10 per cent. It is difficult to justify stopping vein graft surveillance after 1 year even in this selected group.

In summary, legs that have undergone infrainguinal vein grafting are still at a significant risk of developing graft-threatening stenoses more than 1 year after operation. Whether treating these stenoses improves graft patency and limb salvage rates can be determined only by a randomized trial. This is unlikely to happen given the small number of patients involved and the ethical dilemma of observing a vein graft with a critical stenosis. In this series, six of 11 grafts that developed a run-off stenosis more than 12 months after operation had only a single run-off vessel. It would be difficult to justify not treating these critical stenoses.

Acknowledgements

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Marimastat inhibits neointimal thickening in a model of human vein graft stenosis

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Background There is now accumulating evidence that matrix metalloproteinases (MMPs), the physiological mediators of matrix deposition and degradation, play an important role in the development of intimal hyperplasia following arterial bypass. This study investigated the effect of marimastat, an orally active specific MMP inhibitor, on neointima formation in cultured human saphenous vein.

Methods Segments of human saphenous vein obtained from ten patients undergoing arterial bypass surgery were cultured for 14 days in serum-supplemented RPMI medium (controls) or in control medium supplemented with marimastat at three different concentrations (treatment groups). Following culture, half of each segment was prepared for histological examination and MMPs were extracted from the other half for gelatin zymography.

Results Marimastat inhibited neointimal thickening in a concentration-dependent manner; inhibition was significant at 10^{-5} and 10^{-6} mol/l ($P = 0.006$). This observation was paralleled by a significant reduction in the levels of MMP-2 and MMP-9 in the tissues.

Conclusion Marimastat significantly reduced neointimal thickening in this laboratory model. MMP inhibitors may offer a potential therapeutic strategy in the prevention of intimal hyperplasia.

More than 30 per cent of vein grafts develop patency-threatening stenosis in the first year after operation[1]. The underlying pathological lesion is intimal hyperplasia, a condition characterized by excessive smooth muscle cell (SMC) migration and subsequent proliferation[2–5]. A number of studies, principally performed on animals, have emphasized a major role for growth factors and cytokines as SMC mitogens and chemoattractants to modulate this response[6]. As yet, therapeutic agents aimed at inhibiting SMC proliferation have been ineffective clinically[7].

In addition to increased numbers of SMCs, neointimal lesions contain an abundance of extracellular matrix (ECM)[8]. There is now accumulating evidence that degradation of the ECM in response to growth factors is necessary to permit proliferation and movement of SMCs. The SMCs in the normal vasculature are surrounded by a basement membrane and embedded within a matrix of connective tissue[9] which maintains them in a quiescent and differentiated state with a low replication rate[10]. It has been shown by Southgate and colleagues[11,12] that SMC migration and proliferation requires degradation of matrix proteins and that this process is accomplished by secretion of specific matrix-degrading enzymes from the SMCs themselves. Vascular SMCs have the ability to digest all components of the ECM through production and secretion of matrix metalloproteinases (MMPs)[13–15].

The MMPs are a family of zinc-dependent enzymes which act as the principal physiological mediators of ECM degradation. They are classified according to their substrate specificity and include the collagenases, stromelysins and gelatinases which are able to interact to degrade all the components of the ECM. Their activity is tightly regulated by specific tissue inhibitors of metalloproteinases (TIMPs)[16]. The gelatinases, which comprise gelatinase A (MMP-2) and gelatinase B (MMP-9), efficiently degrade type IV collagen[17], the major structural component of the basement membrane[18]. Therefore gelatinases in particular are implicated in removing the first ECM barrier to migration and proliferation of SMCs.

To support this hypothesis, Southgate *et al.*[11] have detected gelatinase, but not stromelysin or collagenase activity, in rabbit SMCs, and have also shown that migration and proliferation from cultured explants is inhibited by specific, synthetic MMP inhibitors. Other animal studies have suggested that MMPs may mediate tissue remodelling and therefore play a crucial role in the development of intimal hyperplasia following arterial injury[19,20]. Although evidence from animal studies is accumulating, there are considerably fewer data from human tissue to support a role for MMPs in human intimal hyperplasia.

The present study used organ culture of human saphenous vein, a well validated laboratory model of human intimal hyperplasia[8,21,22]. Fabunmi and colleagues[23] have previously shown that gelatinase A and gelatinase B are upregulated after angioplasty in the pig, and that similar upregulation of gelatinase B also occurs during neointima formation in organ cultures of human saphenous vein. The latter observation has recently been confirmed in this laboratory[24]. Raised levels of MMPs may play a significant role in the development of human vein graft stenosis. Inhibition of these enzymes could offer a potential therapeutic strategy to prevent intimal hyperplasia[24]. The present study investigated whether marimastat (a non-selective MMP inhibitor) is able to reduce neointima formation in cultured human long saphenous vein. Levels of MMP-2 and MMP-9 were measured in marimastat-treated and untreated vein segments.

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Patients and methods

Culture method

Segments of the long saphenous vein were obtained from ten patients undergoing arterial bypass grafting and prepared for culture as described previously[8]. For each patient, three individual segments of vein were prepared and cultured. One segment served as a control and the remaining two were cultured in medium supplemented with marimastat at a therapeutic (10^{-6} mol/l) or supratherapeutic (10^{-5} mol/l) concentration. In five patients sufficient vein was available to culture a further segment at a lower concentration of marimastat (10^{-7} mol/l). Culture medium and drugs were replaced every 2 days and at the end of the 14-day culture interval the segments were divided into two equal halves. One half was fixed in 4 per cent paraformaldehyde for 18 h, processed, embedded in paraffin and cut in sections 4 μm thick. The remaining half was immediately snap-frozen in liquid nitrogen for subsequent metalloproteinase extraction and gelatin zymography.

Gelatin zymography

Metalloproteinases were extracted from frozen tissues by a method described previously[25,26]. The protein concentration of each sample was determined by the method of Bradford[27] and normalized to 0·9 mg/ml. Zymography was performed on each sample by non-reducing electrophoresis through a 10 per cent sodium dodecyl sulphate–polyacrylamide gel impregnated with 1 mg/ml gelatin as described previously[26]. Proteinases were visualized as clear bands of lysis against a dark background of intact substrate. The molecular weight of each band was estimated by comparison with known molecular weight standards (Bio-Rad, Hemel Hempstead, UK). Inhibition of protease activity was used to confirm the nature of the protease being detected on the zymograms. Ethylenediamine tetra-acetic acid 20 mmol/l, 1,10-phenanthroline 5 mmol/l or phenylmethylsulphonylfluoride 1 mmol/l was included in the incubation buffer to confirm the presence of specific MMPs. The relative density of each lytic band was determined from negative photographic images of the gels with an Imagemaster scanning densitometer (Pharmacia LKB, St Albans, UK) and expressed as a product of the optical density and the area of the band. The protein concentration used in this analysis has been shown previously to be within the linear range for densitometric quantification (data not shown). To allow for variation between zymographic gels, samples from within each experimental group were run on the same gel and paired statistics were used in the analysis. No comparisons were made between different gels.

Immunohistochemistry

Paraffin sections 4 μm thick were stained using a monoclonal antismooth muscle actin superimposed with Miller's elastin stain[28] to identify the layers of the vein wall. Measurements of neointimal thickness were made using a computerized image analysis system (Improvision, Coventry, UK) and taking a minimum of 30 measurements across the entire length of two consecutive sections for each vein segment as described previously[8].

Statistical analysis

Neointimal thicknesses are expressed as median (range).

For the zymographic analysis the relative density of gelatinolytic bands was quantified and compared between samples run on the same gel. Relative density was calculated as a ratio with respect to a control (HT-1080 cells, a fibrosarcoma cell line that secretes significant quantities of MMP-2 and MMP-9), and expressed as median and 95 per cent confidence interval (c.i.).

Differences between the groups were analysed using the Wilcoxon paired rank test with significance assumed at the 95 per cent confidence level.

Results

Neointimal thickness

Fig. 1 shows representative histological sections of vein cultured with and without marimastat. During the 14-day culture interval control veins all developed a significant neointima, with a median thickness of 22 (range 16–29) μm. Marimastat at 10^{-5} and 10^{-6} mol/l significantly attenuated neointima formation in a concentration-dependent manner. The median difference

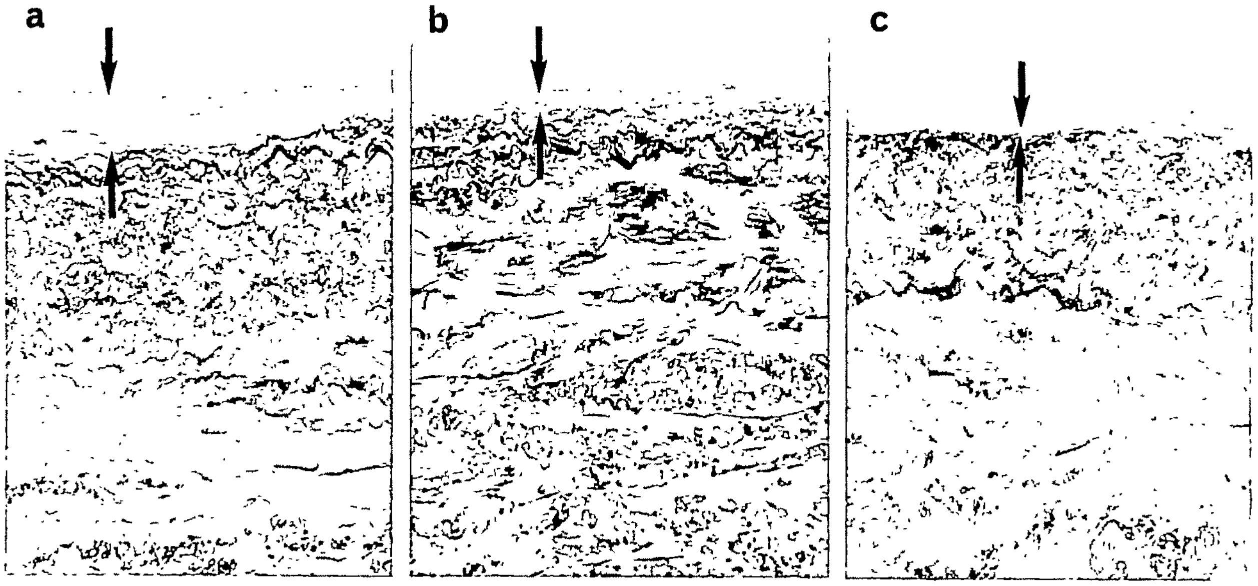

Fig. 1 Sections of cultured vein stained with a combined smooth muscle actin and Miller's elastin stain, showing development of neointima (arrows). Vein segments treated with marimastat 10^{-6} mol/l (b) and 10^{-5} mol/l (c) developed significantly less neointima than control veins (a) ($P = 0·006$, Wilcoxon paired rank test). Original magnification ×160

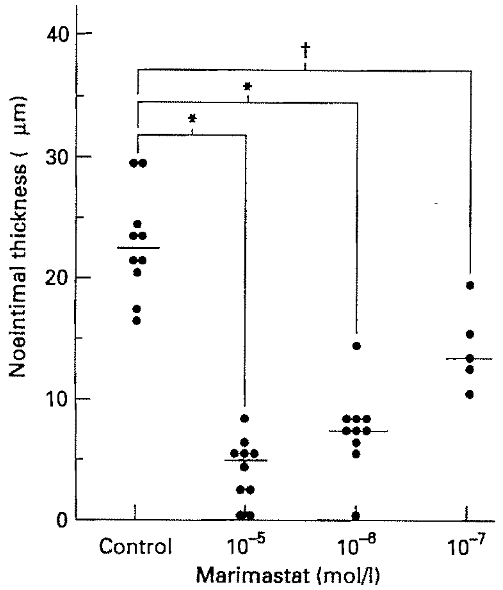

Fig. 2 Scatterplot showing neointimal thickness of control and marimastat-treated veins. Marimastat reduced neointimal thickness in a dose-dependent manner. Horizontal bars represent the median value for each treatment group. $^*P = 0{\cdot}006$, $^\dagger P = 0{\cdot}059$ (Wilcoxon paired rank test)

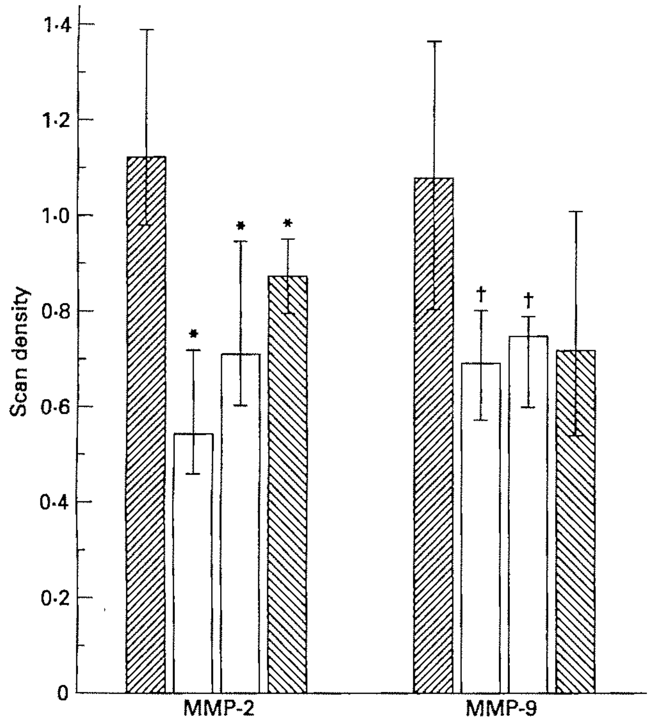

Fig. 3 Protease activity of vein homogenates cultured in medium without (▨) or with marimastat 10^{-5} mol/l (☐), 10^{-6} mol/l (☐) or 10^{-7} mol/l (▨). Values are median (95 per cent confidence interval). MMP, matrix metalloproteinase. $^*P < 0{\cdot}02$, $^\dagger P = 0{\cdot}03$ *versus* control (Wilcoxon paired rank test)

in neointimal thickness between controls and veins cultured in marimastat 10^{-5} mol/l was 18·5 (95 per cent c.i. 15·0–22·0) µm ($P = 0{\cdot}006$); that between controls and segments cultured in marimastat 10^{-6} mol/l was 15·5 (95 per cent c.i. 11·5–19·0) µm ($P = 0{\cdot}006$). A reduction in neointimal thickness was observed in the group treated with marimastat 10^{-7} mol/l, which was not significant (*Fig. 2*).

Gelatin zymography

Densitometric values were expressed as a ratio to a control (HT-1080 cells). The median ratio for MMP-2 in controls was 1·12 (range 0·79–1·73) and that for MMP-9 was 1·08 (range 0·57–1·57). Levels of MMP-9 were significantly reduced in vein cultured with marimastat at 10^{-5} and 10^{-6} mol/l, but not at 10^{-7} mol/l. Marimastat reduced MMP-2 levels at all concentrations studied (*Fig. 3*).

Discussion

This study demonstrates that pharmacological doses of marimastat inhibit neointima formation in cultured human saphenous vein with a concomitant reduction in the levels of MMP-2 and MMP-9 in the tissues. It has been shown previously that tissue levels of MMP-2 and MMP-9 are upregulated after angioplasty in the pig[29] and rat[19], in experimental lesions of cholesterol-fed rabbits[30], in human atherosclerotic plaques[31,32], and in organ cultures of human saphenous vein[24,33]. Blockade of MMP activity may therefore inhibit the SMC response to injury. This hypothesis is supported by the observations of Forough *et al.*[34], who showed that rat SMCs overexpressing baboon TIMP-1 are inhibited in their ability to migrate and proliferate.

The present study used a laboratory model which relies upon the secretion of endothelium-derived growth factors to stimulate SMC migration and proliferation in a paracrine manner[22]. The authors have recently shown that in this model cultured veins produced raised levels of MMP-9 and a trend towards increased activation of MMP-2[24]. These observations are in agreement with those of George *et al.*[33], who also demonstrated increased secretion of MMP-9 and MMP-2 in venous segments cultured for 12 days compared with that of freshly isolated tissue. The main drawback of the organ culture model is that it is a no-flow system, and 'disturbed' flow conditions *in vivo* have been shown to have a major influence on the development of intimal hyperplasia[35,36]. It will be important to study the effects of marimastat under flow conditions using a laboratory model[37].

MMPs are normally tightly regulated by TIMPs[38], thus maintaining a balance between matrix degradation and deposition. An imbalance between MMPs and associated TIMPs may play a significant role in the development of intimal hyperplasia. However, TIMPs are probably not suitable as pharmacological agents because of their short half-life *in vivo*.

Marimastat is a synthetic, low molecular weight MMP inhibitor with a collagen-mimicking hydroxamate structure which facilitates chelation of the zinc ion in the active site of MMPs[39]. Marimastat and its predecessor batimastat both inhibit MMPs potently and specifically[39]. Batimastat was the first synthetic MMP inhibitor-studied in patients with advanced malignancy. Its usefulness was limited by its extremely poor water solubility. In contrast, marimastat is active orally and is the first MMP inhibitor to enter clinical trials for patients with metastatic disease[40].

The results of the present study are in agreement with the findings of Bendeck *et al.*[19], who showed a 97 per cent reduction in the early migration of SMCs when an MMP inhibitor was administered systemically following angioplasty of the rat artery, with an accompanying reduction in neointimal hyperplasia. However, in the long term such lesions underwent a 'catch-up' phenomenon as a result of increased SMC proliferation[20]. This was not an observation made in the present study, possibly because of the short culture time or because of fundamental differences between animal and human tissue. Although the 'treatment time' in this study was only 14 days, the changes occurring in this model closely resemble those that occur *in vivo* over several months[8] (SMC phenotypic change, migration, proliferation and ECM deposition). To achieve a significant therapeutic effect of marimastat in the prevention of intimal hyperplasia, it is likely that longer-term therapy would be required.

Marimastat is currently being studied in multicentre clinical trials for a variety of cancers, and has been shown to be maximally effective at a dose of 10 mg twice daily[40]. The drug is generally well tolerated but the principal side-effect noted after prolonged treatment was pain and tenderness in muscles, tendons and joints which affected about 30 per cent of patients after 5 months of treatment[39]. Fortunately these side-effects were completely reversible. It has been possible to achieve biologically active plasma concentrations of marimastat that are well tolerated in patients with cancer[39].

This *in vitro* study has demonstrated significant inhibition of neointima formation *in vitro* by marimastat. The pharmacological profile and bioavailability of marimastat make it attractive for clinical trials investigating the effect of MMP inhibition on the development of neointimal hyperplasia.

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Early results of a randomized trial of rifampicin-bonded Dacron grafts for extra-anatomic vascular reconstruction

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Background The aim of this study was to determine whether the routine use of an antibiotic-bonded gelatin-coated Dacron graft could reduce the incidence of prosthetic graft infection. Extra-anatomic grafts were chosen for study as they have the highest risk of graft infection. This paper reports early results up to 1 month after surgery.

Methods This multicentre study involved 14 vascular units in the UK. A total of 257 patients underwent extra-anatomic bypass. Patients were randomized to rifampicin bonding (1 mg/ml rifampicin soak for 15 min before graft insertion) or a control group. Routine three-dose antibiotic prophylaxis was administered to patients in both groups.

Results There were 178 men and 79 women of median age 69 (range 43–92) years. Rifampicin-bonded ($n = 123$) and control ($n = 134$) groups were well matched for clinical details, risk factors and operative techniques. No side-effects were noted from rifampicin bonding. Only one patient (in the control group) developed a graft infection and this proved fatal. There were no significant differences between bonded and unbonded grafts in terms of perioperative mortality rate (9 and 5 per cent respectively), median hospital stay (10 days for both groups), total infective complications (15 and 21 per cent respectively) or need for postoperative antibiotics (13 and 18 per cent respectively).

Conclusion Early results from this study have not identified any significant advantage in the routine use of rifampicin bonding, but the rate of graft infection was very low (0·4 per cent). Gelatin coating alone may provide protection against infection. Definitive recommendations about the role of antibiotic bonding cannot be made until longer follow-up becomes available.

About one in 50 implanted prosthetic vascular grafts becomes infected with bacteria and if the graft is anastomosed to the aorta this results in a mortality rate of nearly 50 per cent[1]. As the number of prosthetic grafts inserted increases every year, so the prevalence of serious infection rises. However, because of the low numbers of patients treated in individual units, there is little evidence-based research into preventing infection. It is known that the majority of bacteria are implanted at the time of original surgery and measures to reduce graft infection should be directed to this stage[1,2].

One theoretical way of reducing graft infection is to bond an antibiotic to the surface of the graft. The bond needs to be strong enough to prevent antibiotic dislodgement at arterial pressure and flow, and durable enough to last through the perioperative period. The antibiotic should be safe, non-toxic and have appropriate antibacterial activity. Rifampicin has been shown to become attached through ionic bonding to the surface of gelatin-coated Dacron (Vascutek, Renfrewshire, UK) grafts both *in vitro*[3] and *in vivo*[4,5]. Rifampicin has excellent activity against staphylococci, the principal cause of graft infection[6].

The aim of this study was to determine whether the routine use of a rifampicin-coated Dacron graft would reduce the incidence of early and late graft infection. Extra-anatomic grafts were chosen as the model for study because they are documented to have the highest incidence of graft infection (up to 10 per cent in publications available at the time the study was planned)[7,8]. Patients who needed an extra-anatomic bypass were randomly allocated to receive a rifampicin-bonded graft or a similar but unbonded graft. This report describes the methodology and early results up to 1 month after surgery

Patients and methods

This was a multicentre study involving 14 vascular surgical departments in the UK and Ireland. All centres were members of the Joint Vascular Research Group (see Acknowledgements). The protocol was agreed by the Group and ratified by the local hospital ethics committee in each centre. It was calculated that to detect a 50 per cent reduction in graft infection 250 patients would need to be randomized. All patients gave written informed consent. Consecutive patients who required an extra-anatomic (cross-iliofemoral, femorofemoral or axillofemoral) graft in each centre were recruited. Patients willing to participate were excluded only if known to be allergic to rifampicin.

Some 257 patients were randomized, a median of 13 (range 3–56) per centre. There were 178 men and 79 women of median age 69 (range 43–92) years. Randomization was carried out on the day of operation using sealed envelopes, with block randomization in larger vascular centres; the remainder used a central telephone number to obtain randomization based on computer-generated random numbers. A total of 123 patients were randomized to receive a rifampicin-bonded graft and 134 were controls. The preoperative risk factors and indications for surgery were well matched between the patients who had bonded and unbonded grafts (*Tables 1* and *2*).

All patients had extra-anatomic bypass using a gelatin-coated Dacron graft (Gelsoft or Gelseal; Sulzer Vascutek, Renfrewshire, UK). For patients randomized to rifampicin bonding, the graft was soaked in a solution of rifampicin 1 mg/ml for 15 min before insertion. Surgical technique was standardized within each centre. All patients received three perioperative doses of an

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Table 1 Clinical details

	Rifampicin bonded ($n=123$)	Unbonded ($n=134$)	Total ($n=257$)
Men	86	92	178
Women	37	42	79
Median (range) age (years)	71 (50–92)	68 (43–87)	69 (43–92)
Indication for surgery			
Claudication	56	61	117
Ischaemic rest pain	35	37	72
Skin necrosis	23	29	52
Acute ischaemia	9	7	16

Table 2 Preoperative risk factors for infection

	Rifampicin bonded ($n=123$)	Unbonded ($n=134$)	Total ($n=257$)
Diabetes	17	10	27
Steroids	2	5	7
Obesity	10	11	21
Distal skin necrosis	21	21	42
Urgent operation	30	22	52
Reoperation	9	11	20
Other	1	2	3
No risk factor	62 (50)	70 (52)	132 (51)
One risk factor	36 (29)	46 (34)	82 (32)
Two or more risk factors	25 (20)	18 (13)	43 (17)

Values in parentheses are percentages

Table 3 Operative details

	Rifampicin bonded ($n=123$)	Unbonded ($n=134$)	Total ($n=257$)
Femorofemoral	67	81	148
Axillofemoral	42	39	81
Cross-iliofemoral	14	14	28
Consultant	90	99	189
Surgical trainee	33	35	68

Table 4 Postoperative complications

	Rifampicin bonded ($n=123$)	Unbonded ($n=134$)	Total ($n=257$)
Wound erythema (grade I)*	7	13	20
Wound discharge (grade II)*	9	9	18
Wound dehiscence (grade III)*	3	5	8
Graft infection (grade III)*	0	1	1
Total	19 (15)	28 (21)	47 (18)
Second course of antibiotics (any cause)	16 (13)	24 (18)	40 (16)
Delayed discharge from hospital (any cause)	10 (8)	15 (11)	25 (10)

Values in parentheses are percentages. *Szilagyi infection grade[9]

intravenous antibiotic according to local protocol; most surgeons employed a cephalosporin or co-amoxiclav. Operative details were well matched between the groups (*Table 3*).

Outcome was recorded prospectively on specially designed pro formas and returned for central collation. Infective complications were graded according to the schedule of Szilagyi: grade I, mild erythema or inflammation; grade II, discharge of pus and frank infection; grade III, graft infection or wound dehiscence[9]. Patients were reviewed 1 month after hospital discharge and will be followed at intervals of 6 months for 2 years.

Statistical analysis was carried out with χ^2 testing, significance was taken at the 5 per cent level.

Results

Operative details in the 257 randomized patients are recorded in *Table 3*. No side-effects were noted from rifampicin bonding. A total of 200 patients made an uncomplicated recovery: 95 (77 per cent) of 123 with bonded and 105 (78 per cent) of 134 with unbonded grafts. Median duration of hospital stay was 10 days in both groups (range 1–79 days for the whole series).

There were 18 (7 per cent) perioperative deaths: 11 (9 per cent) with bonded and seven (5 per cent) with unbonded grafts. Fifteen patients died within 30 days, one after hospital discharge (pulmonary embolism 4 weeks after surgery). One patient died from sepsis 37 days after surgery and one from multiorgan failure 10 weeks after surgery, both without leaving hospital. One patient was readmitted shortly after discharge with an acute abdomen and died despite surgery, 5 weeks after initial operation. The majority of the deaths were due to myocardial infarction (five patients) or renal failure (four); these were associated with early graft thrombosis in four cases. The mortality rate for each procedure was: axillofemoral, 12 (15 per cent) of 81; cross-iliofemoral, three (11 per cent) of 28; and femorofemoral, three (2 per cent) of 148. The mortality rate was 14 (10 per cent) of 140 in patients who had surgery for critical or acute ischaemia and four (3 per cent) of 117 in those with claudication ($\chi^2 = 4{\cdot}24$, 1 d.f., $P = 0{\cdot}04$). In addition to the four who died, 12 other patients had grafts that thrombosed within 30 days of surgery (overall early thrombosis rate 6 per cent).

The rate of infective complications was similar in both groups (*Table 4*). There was only one graft infection (unbonded graft) which resulted in death from sepsis 37 days after operation. An 84-year-old woman had a cross-iliofemoral graft for critical ischaemia. The groin wounds dehisced and the patient died from septicaemia with a patent but infected graft. The principal infective organism, isolated on several occasions, was *Staphylococcus aureus* (haemolytic streptococci were also cultured). The total number of infective wound complications was greater in patients with one or more preoperative risk factor for infection (33 (26 per cent) of 125) than in patients with none (13 (10 per cent) of 132) ($\chi^2 = 11{\cdot}97$, 1 d.f., $P = 0{\cdot}0005$). If only the 125 patients with preoperative risk factors were evaluated, the rate of infective wound complications remained similar: 14 (23 per cent) of 61 patients with bonded grafts compared with 19 (30 per cent) of 64 with unbonded grafts (P not significant)

Discussion

Any study evaluating the rate of prosthetic vascular graft infection has to have a follow-up of several years to be meaningful. The reason for publishing these preliminary findings is that initial results from another randomized comparison of rifampicin-bonded grafts (European study)[10] suggested that antibiotic bonding reduced the rate of local wound complications. There are two other ongoing randomized trials of rifampicin bonding, the European study and an Italian study[11], both of which included all varieties of prosthetic grafts in contrast to the present trial which is concentrating on higher-risk extra-anatomic grafts. Two-year results from the Italian study showed similar rates of graft infection in each group: 2·3 per cent for bonded and 1·7 per cent for unbonded grafts. The European study has yet to report late graft infection data.

The present study has also shown small but non-significant reductions in total wound complications, delayed hospital discharge and postoperative antibiotic requirements. The only adverse outcome was a higher mortality rate in patients with bonded grafts, although it is unlikely any deaths could be related to the bonding procedure. Similar to other reports on extra-anatomic bypass, the mortality rate was higher in patients who had axillofemoral bypass or surgery for critical ischaemia.

The rate of early graft infection was expected to be much higher. Based on previous publications, a graft infection rate of up to 10 per cent was expected, half within the first 30 days[7,8]. The early graft infection rate of one (0·4 per cent) in 257 patients is similar to that in the European study (0·3 per cent for bonded and 0·6 per cent for unbonded grafts)[10] and makes it unlikely that any of the present studies will ever report a sufficiently high event rate to show a statistically different performance between the two grafts, based on known information about the incidence of late graft infection[12]. A possible explanation might be that gelatin coating itself offers protection against infection. It is known that different prosthetic grafts have different susceptibilities to infection[13]. Longer follow-up is required to help answer these points.

The importance of antibiotic bonding in the prevention of graft infection remains uncertain. Animal experiments have shown that rifampicin remains bound to gelatin-coated Dacron grafts in an active concentration for at least 72 h[4,5]. Strachan *et al.*[6] reported a patient who died 21 days after operation whose rifampicin graft still had demonstrable antibacterial activity. Gelatin-coated grafts are presently the only ones known to retain rifampicin when placed in the arterial circulation. In other experiments rifampicin-bonded grafts have been shown to afford some protection against bacterial implantation[14–16]. They also reduced the rate of reinfection when used for *in situ* replacement in an animal model of established graft infection[17]. There is no evidence that bonding confers any increase in thrombogenicity in this or experimental studies[18], nor that resistance to rifampicin develops[19].

In clinical studies, bonded grafts have been used for *in situ* replacement of infected aortic grafts and mycotic aneurysms with promising early results[20,21]. This might be particularly useful in patients with aortic graft infection in whom conventional procedures carry a high risk of morbidity and mortality[22]. A significant proportion of graft infection arises as a result of direct spread from adjacent wound infection. As in the present study, preoperative risk factor analysis can be used to identify high-risk patients and Strachan[2] has evolved a policy of using rifampicin-soaked grafts in these patients. This is in contrast to the present study which aimed to determine whether bonded grafts should be used routinely for all patients having insertion of a prosthetic graft. In the present study, subgroup analysis of high-risk patients with preoperative risk factors did not find any advantage for rifampicin bonding, although the numbers were small. There is also debate about the concentration of rifampicin that should be used (1 mg/ml in this and all the other randomized studies). It has been suggested that a much higher concentration (60 mg/ml) might be used, particularly for *in situ* replacement of an infected graft[2].

Final recommendations about the role of antibiotic bonding for prosthetic grafts may be made only when the late results of the three present randomized trials are eventually reported. Even then, the studies are unlikely to have sufficient power to show a statistically significant advantage for rifampicin soaking. Until then, the policy of using a bonded gelatin-coated graft in patients known to be at high risk seems sensible. No disadvantages have been identified and rifampicin is cheap. This antibiotic is principally active against Gram-positive organisms and may not have the ideal antibiotic spectrum, particularly as Gram-negative infections appear to be increasing. Other antibiotics might be investigated. Meanwhile the rifampicin–gelatin combination is the only graft technique known to survive arterial pressure and flow. The simplicity of the method is appealing.

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Outcome in patients with a large abdominal aortic aneurysm considered unfit for surgery

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Background The risk of rupture of large abdominal aortic aneurysms (AAAs) remains uncertain. This study aimed to provide data to help decide whether or not to operate on high-risk patients.

Methods Clinicians were asked to refer all patients with an AAA, even if unfit or elderly. One hundred and ninety-two patients with an intact AAA of 5 cm or greater in diameter were seen in 9 years; 59 had no elective operation and follow-up data were available for 57 at a minimum of 2 years. Initial AAA diameters were 5·0–5·9 cm ($n = 25$) and 6·0 cm or more ($n = 32$). Survival curves were constructed for both groups.

Results At the end of the study 50 of 57 patients had died. Median survival was 18 (range 1–90) months. Twenty (35 per cent) suffered rupture at a median interval of 18 (range 1–38) months. The risk of rupture within 3 years was 28 (95 per cent confidence interval 12–49) per cent for 5·0–5·9-cm AAAs and 41 (24–59) per cent for AAAs of 6 cm or greater. In 133 elective AAA operations in fit patients the 30-day mortality rate was 3 per cent.

Conclusion The risk of rupture within 3 years of diagnosis of an AAA of 5 cm or greater exceeds the expected operative mortality rate for fit patients. However, the majority of patients unfit for surgery died from other causes, and only a few would have benefited from aneurysm repair.

Decisions on the treatment of an intact abdominal aortic aneurysm (AAA) are based on an estimate of the risk of death from rupture weighed against the expected mortality and morbidity rates associated with operation. Advances in anaesthetic and intensive care support, and new techniques of aortic replacement, make it possible to offer treatment to patients previously considered unfit[1]. Balancing risk and benefit in such patients requires knowledge of the natural history of AAA. Screening programmes have added some information on smaller aneurysms[2] but there is a lack of satisfactory data on the prognosis of larger AAAs[3].

To study the natural history, the referral of all patients with an AAA was encouraged even if they were not considered candidates for operation. This paper records a consecutive series of patients with an aneurysm greater than 5 cm in diameter, with particular emphasis on the clinical outcome for those not undergoing operation.

Patients and methods

Basic details on all patients were recorded prospectively at the time of referral, and operations were recorded as part of an ongoing audit. Patients who did not have aneurysm repair were traced by retrospective review of medical notes and contact with general practitioners, patients or relatives.

During 9 years (May 1985 to April 1994) 192 patients with an intact infrarenal AAA of 5 cm or more in anteroposterior or transverse diameter were referred to one surgeon at a district hospital serving a population of approximately 250 000. Minimum follow-up was 2 years. One hundred and thirty-three patients underwent elective operation for an intact aneurysm. Selection was based on clinical judgement using no predetermined criteria. This group included patients who had an urgent operation for symptoms which developed after a period of observation.

Fifty-nine patients were rejected for elective operation. Three later had an emergency operation for rupture. The cause of death, or confirmation of survival, was obtained for 57 of 59 patients; two were lost to follow-up. Of 50 known deaths, information was available from hospital, general practitioner or coroners' records in 47 cases, and from death certificates only in three. Autopsy data were available for seven patients.

For analysis, patients who did not have aneurysm repair were divided into two groups: those with aneurysms of 5·0–5·9 cm and patients with an AAA of 6·0 cm or greater. The initial size of the aneurysm was the sole basis for this grouping; serial measurements were generally not done. Survival was calculated by the Kaplan–Meier method.

Results

The mean age of patients who had aneurysm repair ($n = 133$) was 73 (range 56–85) years whereas for non-operated patients ($n = 57$) it was 81 (range 69–93) years. Patients over 80 years old comprised 22 per cent of all referrals. The elective operation rate in octogenarians was eight (19 per cent) of 43 compared with 125 (84 per cent) of 149 for patients aged under 80 years. In 133 operations for an intact AAA, the 30-day mortality rate was 3 per cent (four patients) with no deaths among eight octogenarians.

The main reasons for denying AAA repair were: cardiovascular disease (25 patients), 'old age' (15), malignancy (eight), respiratory disease (six) and patients' wishes (three). Patients rejected because of 'old age' (mean 85 years) were assessed on functional state, not absolute age. Rejection for patients with aneurysms over 6 cm implied more serious contraindications.

At the close of the study 50 of 57 patients who did not have aneurysm repair had died. Three patients had emergency operation for rupture, one of whom survived, 1 month after refusing surgery for an aneurysm greater than 6 cm in diameter. On the Kaplan–Meier survival

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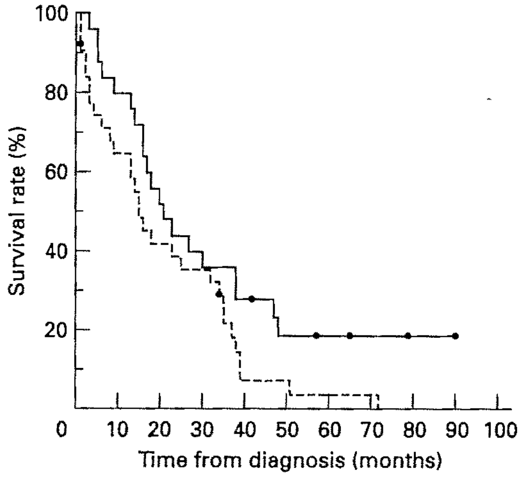

No. at risk							
AAA 5·0–5·9 cm	25	20	14	10	7	4	3
AAA ≥ 6 cm	32	20	13	11	2	1	1

Fig. 1 Kaplan–Meier survival curves for patients with an abdominal aortic aneurysm (AAA) of 5·0–5·9 cm (———) or 6·0 cm or greater (– – –). The symbols (●) indicate 'censored' data for six patients alive at the end of the study and for one patient (also still alive) at the time of rupture

Table 2 Interval to rupture

Interval within which rupture occurred	Size at entry (cm)	Time until rupture (months)	Cumulative percentage ruptured*
AAA 5·0–5·9 cm			
1 year	5·7	6	8 (1–26)
	5·5	9	
2 years	5·6	18	24 (9–45)
	5·0	20	
	5·4	21	
	5·5	23	
3 years	5·5	30	28 (12–49)
AAA ≥6·0 cm			
1 year	8·5	1	16 (5–33)
	14·0	2	
	9·5	3	
	7·0	4	
	7·0	8	
2 years	8·0	13	28 (14–47)
	6·0	15	
	8·2	16	
	8·0	18	
3 years	9·0	25	38 (21–56)
	7·0	32	
	6·6	34	
4 years	6·3	38	41 (24–59)

*Values in parentheses are 95 per cent confidence intervals. AAA, abdominal aortic aneurysm

curve this patient appears as 'censored' at 1 month, since rupture of the aneurysm was considered an endpoint.

The median survival was 21 months in patients with AAA 5·0–5·9 cm in diameter and 15 months for those with an aneurysm of 6 cm and above (*Fig. 1*). A minority of patients survived for more than 3 years. Nine of 25 patients with a 5·0–5·9-cm AAA survived 3 years, five of whom were alive at the end of the study, the longest survivor at 90 months. For AAA of 6 cm and over, six of 32 patients were alive at 3 years (excluding one survivor from rupture); the longest survivor died at 6 years.

Table 1 shows details of the two groups and the causes of death. Twenty patients (35 per cent) suffered a ruptured AAA at a median interval of 18 (range 1–38) months from diagnosis. *Table 2* shows details of each aneurysm that ruptured including initial size and interval until rupture. The cumulative rupture rate for smaller AAAs (5·0–5·9 cm) was 28 (95 per cent confidence interval 12–49) per cent; that for AAAs of 6 cm or greater was 41 (24–59) per cent. In addition to known ruptures, three patients died suddenly and on review of their records it was possible that death might have been due to undiagnosed rupture. The remaining deaths were attributed to the following causes: cardiovascular disease (11 patients), respiratory disease (seven), malignancy (six), renal failure (one), perforated viscus (one), sepsis after amputation (one) and cachexia (one). Of eight patients who had malignancy when rejected for surgery, one died from a ruptured aneurysm, five died from malignancy at 1, 3, 5, 13 and 27 months and two died from other causes.

Table 1 Patient details and cause of death

	Aneurysm size (cm)	
	5·0–5·9	≥6·0
Total no. of patients	25	32
Mean age (years)	79	82†
Sex ratio (M:F)	18:7	25:7
Mean AAA size (cm)	5·4	7·3
Rupture	7	13*
Deaths		
Cause uncertain	2	1
Other disease	11	17
Alive	5	2*

*One patient survived rupture. AAA, abdominal aortic aneurysm. †$P < 0.05$ *versus* 5·0–5·9-cm AAA (Student's *t* test)

Discussion

Patients denied AAA repair had a limited life expectancy, so 35 per cent was a minimum estimate of the risk of rupture. The majority died from other diseases but, surprisingly, 26 per cent survived for more than 3 years.

The maximum aortic diameter is commonly used for operative decision making[2,4] although the anterior–posterior diameter may be a better predictor of rupture[5], is more repeatable[6] and is therefore the basis of the UK Small Aneurysm Trial[7].

The number of patients in this study was small for statistical analysis, but this is the largest series with complete follow-up of untreated aneurysms of 5 cm or greater in the past 25 years. Two larger series, conducted before the introduction of ultrasonography, reported deaths from rupture in 32 and 36 per cent of patients[8,9]. Recent series have been small and have included few ruptures, varying from seven to 19; sometimes patients with acute expansion were included[4,5,10–14]. These papers reported rupture rates for aneurysms of more than 5 cm which varied from 23 to 41 per cent, with annual risks for 5·0–5·9-cm AAAs estimated at between 3 and 11 per cent. In the present series there was a 24 per cent incidence of rupture in the first 2 years from diagnosis of an aneurysm of 5·0–5·9 cm, although some may have enlarged further before rupture.

High rates of rupture may be specific to elderly patients with co-morbidity. Chronic obstructive airway disease is a predictor of rupture[5], and old age, cardiac disease and stroke are associated with rapid expansion[15] but there is no clear evidence that the risk of rupture is less in younger, fitter patients. The present data do not help identify patients likely to suffer early rupture or those likely to survive for long intervals.

Two-thirds of the present patients would not have benefited from operation because they were either destined to die from other causes or to survive for between 3 and 7 years. Morbidity and deaths would have resulted from aggressive surgery in this poor-risk group and less than one-third of the patients would have been helped.

Some authors recommend ultrasonography every 3 months for AAAs of 5 cm or greater, reserving operation for aneurysms that expand by 1 cm or more per year, or reach 6 cm in maximum diameter, or cause symptoms[2,16,17]. Expansion by 1 cm or more may occur in more than half such patients[15]. Longer intervals between scans may be risky. In one study six of ten ruptures occurred within 6 months of ultrasonography that diagnosed an aneurysm of 5·0–5·6 cm[14].

The mortality rate following AAA repair depends partly on case selection. A recent study in the Oxford region found that one-third of patients with aneurysms above 5 cm were judged unfit for operation[18]. The decision to operate on less fit patients remains a problem that requires better predictive criteria.

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Glutaraldehyde as a possible cause of diarrhoea after sigmoidoscopy

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Background An outbreak of proctitis at the start of a colorectal cancer screening programme utilizing flexible sigmoidoscopy prompted scrutiny of the incidence of this complication and the role of glutaraldehyde in its aetiology.

Methods Questionnaires completed 1 day and 3 months after sigmoidoscopy were reviewed for 388 patients, and glutaraldehyde levels in the recycled rinse water of the endoscope washing machine were measured. The incidence of symptoms in the subsequent 612 patients after installation of a washer that does not recycle rinse water was examined.

Results Five patients (1·3 per cent) presented to hospital with bloody diarrhoea occurring immediately after a normal flexible sigmoidoscopy. Repeat examination confirmed the presence of proctitis. Symptoms subsided rapidly with either no treatment or steroid enemas. Eight additional patients (2·1 per cent) recorded similar problems but received no treatment and the symptoms settled spontaneously. Glutaraldehyde levels rose progressively in the rinse water after each wash cycle with 2 per cent glutaraldehyde solution. Only one possible case of proctitis (0·2 per cent) was identified from the questionnaires completed by 612 patients after changing to a washer that did not recycle the rinse water.

Conclusion These observations should prompt the careful assessment of cleaning techniques. The use of washing machines that do not recycle rinse water may avoid this complication.

Glutaraldehyde is a recommended disinfectant widely used in endoscopy units. Its toxicity after inhalation and cutaneous exposure is well recognized and is due to both direct irritation and hypersensitivity reactions[1]. It causes colitis in animal models[2] and has been linked to proctocolitis occurring after endoscopic procedures[2–4]. This has been attributed to a poor cleaning technique[2] resulting in glutaraldehyde retention in the endoscope and connecting tubing[4]. Although it is strongly implicated, previous reports have not measured the actual levels of glutaraldehyde; however, its accumulation in recycled rinse water has been inferred by indirect measurement[5]. This study examined an outbreak of proctitis after sigmoidoscopy and associated it with increasing levels of glutaraldehyde in recycled rinse water.

Patients and methods

An outbreak of bloody diarrhoea occurring within 24 h of flexible sigmoidoscopy at a colorectal screening centre prompted scrutiny of the incidence of this complication and the role of glutaraldehyde in its aetiology. The Flexiscope Screening Trial is a multicentre study of single flexible sigmoidoscopic examination in patients aged between 55 and 65 years. The study uses dedicated nursing staff and equipment and all examinations are performed by a single endoscopist (J.M.H.). After identification of the index patients the questionnaires completed routinely 1 day and 3 months after sigmoidoscopy were reviewed. The initial cohort underwent examination with flexible sigmoidoscopes cleaned with the Auto-Disinfector 3 (Keymed, Southend, UK) which recycles the rinse water. Questionnaires were also examined for patients who had endoscopy after the installation of a new washer that does not recycle rinse water (Autoscope F-DT; Labcaire, Clevedon, UK). Questionnaires were scrutinized for symptoms of proctitis occurring within 24 h of the examination, namely bloody diarrhoea, tenesmus and abdominal cramps.

Glutaraldehyde levels in the recycled rinse water of the Auto-Disinfector 3 were measured after each cycle for five consecutive cycles. Glutaraldehyde levels were measured by the quality control laboratory of the West Midlands Regional Health Authority, Birmingham, UK. Levels were determined by derivatization to *bis*-dinitrophenylhydrazone, followed by reverse-phase high-pressure liquid chromatography.

Disinfection protocol

Endoscopes were washed according to European Society of Gastroenterology guidelines[6]. They were prewashed and brushed through with detergent (Hospec; Youngs Detergents, Warrington, UK) then soaked for 10 min in 2 per cent glutaraldehyde (ASEP; Galen, Craigavon, UK) before rinsing in water. Endoscopes were then rinsed again by hand and wiped dry. The washing machine used initially (Auto-Disinfector 3) recycled the rinse water five times before it was changed. The subsequent machine (Autoscope F-DT) used fresh rinse water on each occasion.

Results

Thirteen patients from the first 388 examinations described symptoms consistent with the diagnosis of proctitis. Five of these (1·3 per cent) (mean age 61 years; three men) presented clinically with bloody diarrhoea and tenesmus within 24 h of flexible sigmoidoscopy. Two had polyps which had not been removed and one had a small polyp that had been snared at the time of examination; the remainder were normal. No patient had a history of inflammatory bowel disease, contact with infective diarrhoea, foreign travel or recent antibiotic use. Sigmoidoscopy confirmed the presence of haemorrhagic proctitis, stool cultures were negative and histology showed inflammatory changes consistent with a toxic

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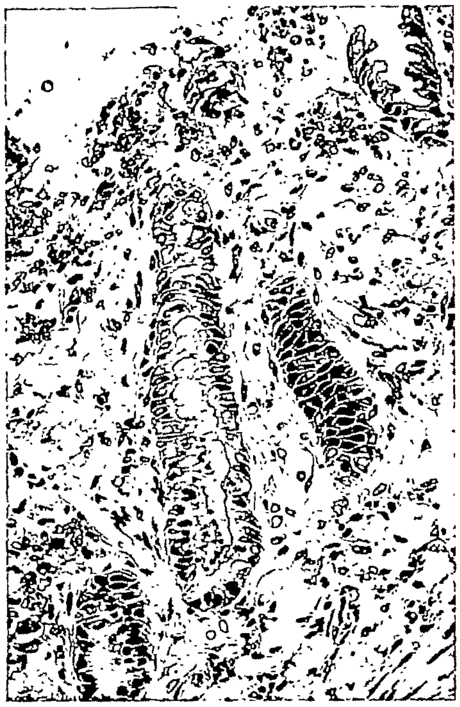

Fig. 1 The mucosa shows vascular congestion with moderate numbers of foamy macrophages indicating crypt damage consistent with toxic colitis. (Haematoxylin and eosin stain. Original magnification ×312)

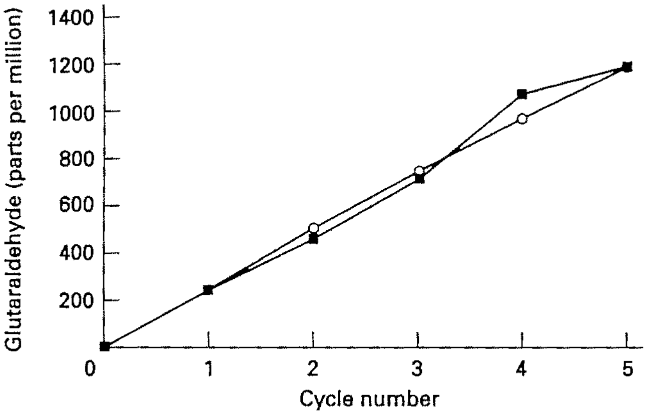

Fig. 2 Glutaraldehyde levels in recycled rinse water reservoir. ○, Run 1; ■, run 2

reaction (*Fig. 1*). All patients settled within 7 days with either no treatment (two patients) or the use of steroid enemas. The eight further patients with proctitis (2·1 per cent) were identified by scrutiny of postexamination questionnaires (mean age 57 years; six men). These subjects did not seek hospital attention and confirmatory sigmoidoscopic evidence was not available.

Postexamination questionnaires from the 612 patients who underwent sigmoidoscopy after the washing machine had been changed revealed only one 58-year-old woman (0·2 per cent) who had experienced symptoms that could be consistent with proctitis, although she did not present clinically ($P < 0·0001$, Fisher's exact test).

Glutaraldehyde levels in the recycled rinse water increased progressively with each wash (*Fig. 2*).

Discussion

The potentially toxic effects of glutaraldehyde on healthcare professionals are widely recognized[1]. Glutaraldehyde causes both cutaneous and mucosal inflammation after direct exposure to as little as 0·2 parts per million[7]. Workers with skin rashes were negative to glutaraldehyde patch testing, indicating a direct toxic effect rather than an allergic reaction. Direct toxicity has been demonstrated clearly in a rodent model in which rectal instillation of 2 per cent glutaraldehyde produced toxic colitis and an appreciable mortality rate[2]. The toxic levels for endoscopic exposure in humans are unknown.

A number of publications have alluded to the role of glutaraldehyde in the aetiology of proctitis after sigmoidoscopy[2,4,8,9] although no unequivocal causality has been established. The incidences in retrospective studies were three of 2400 (0·1 per cent)[10], 21 of 1668 (1·3 per cent)[8] and 14 of 299 (4·7 per cent)[3], compared with 13 of 388 (3·4 per cent) in the present study, of which only five were confirmed sigmoidoscopically.

The manufacturer of the machine that uses recycled rinse water (Keymed) acknowledges the increase in glutaraldehyde levels and recommends rinse water changes after at most five rinses[11]. Only one previous study has measured glutaraldehyde levels in washing fluids[5] and these were measured indirectly by relatively inaccurate methodology. The glutaraldehyde levels measured directly in the present study fall within the machine's specification (Keymed, personal communication). None the less the evidence implicating glutaraldehyde in this case cluster, although circumstantial, is strong. Toxic potential has been clearly demonstrated in both animal and human studies, and when the washing machine was changed no further firmly documented cases occurred. It is likely that increasing levels of glutaraldehyde in recycled rinse water, coupled with unsatisfactory manual rinsing and drying, allow potentially toxic glutaraldehyde concentrations to contact the colorectal mucosa. Previous case series have implicated inadequate processing by a new technician[2] and highlighted the importance of thorough cleaning, flushing and drying, particularly of the insufflation channel[4]. The rapid turnover that is possible and often necessary when dealing with healthy subjects in a screening clinic must not be allowed to compromise these processes.

This study was prompted by presentation of a number of cases after endoscopy. Many probable cases did not present to hospital at all and were presumed to have proctitis on the basis of history alone. It is important that patients with relatively minor but troublesome symptoms are identified as they may highlight inadequate cleaning procedures. In addition to scrupulous adherence to published disinfection protocols, periodic assessment of patients after endoscopy by telephone or postal questionnaire is needed to identify the incidence of proctitis after sigmoidoscopy. If a clinical problem is noted, careful assessment of cleaning techniques is indicated to prevent further cases. The use of washing machines that do not recycle rinse water is likely to limit the incidence of this symptomatically distressing condition.

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Short note

What patients think of day-surgery proctology

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Increasing numbers of surgical procedures are performed as day cases but colorectal surgical practice has been slow to embrace the concept because of perceived problems with postoperative pain management. The purpose of this study was to assess the reaction of patients to a newly instituted day-surgery list dedicated to coloproctology.

Methods

Over 18 months, 129 consecutive patients undergoing day-case general anaesthetic colorectal procedures using propofol infusion for sedation were asked to complete a questionnaire on the first evening and 5 days after operation. Each response was chosen from a five-point scale. The operation was performed by three senior trainees. Minor and intermediate procedures, including haemorrhoidectomy, were performed with meticulous attention to haemostasis.

Results

Questionnaires were completed by 105 patients (81 per cent) (58 men). Mean age was 44 (range 16–76) years. Procedures performed were: haemorrhoidectomy (28), lateral sphincterotomy (17), treatment of fistula *in ano* (13), examination under anaesthesia (14), removal of polyps (eight) and skin tags/warts (ten), excision of pilonidal sinus (eight) and correction of mucosal prolapse (seven).

All but one patient were discharged within 6 h of operation; there were no readmissions following discharge. Eighteen per cent contacted their general practitioner within 72 h, mainly because of bleeding, but only half of these required a visit.

Pain scores diminished over the 5 days after operation. Pain following pilonidal sinus excision or haemorrhoidectomy was greater than that after other operations (*Fig. 1*). Seventy-six per cent thought that postoperative pain was less than or the same as they had expected but 7 per cent thought it would have been reduced if they had stayed in hospital. Within 2 days, 88 per cent of respondents had had a bowel action.

Ninety-three per cent of respondents believed that they had received the correct amount of information before surgery. After surgery and before discharge 62 per cent felt they had been given sufficient information from the surgeon about what was done and what to expect afterwards; 86 per cent thought they received enough information from the nurses.

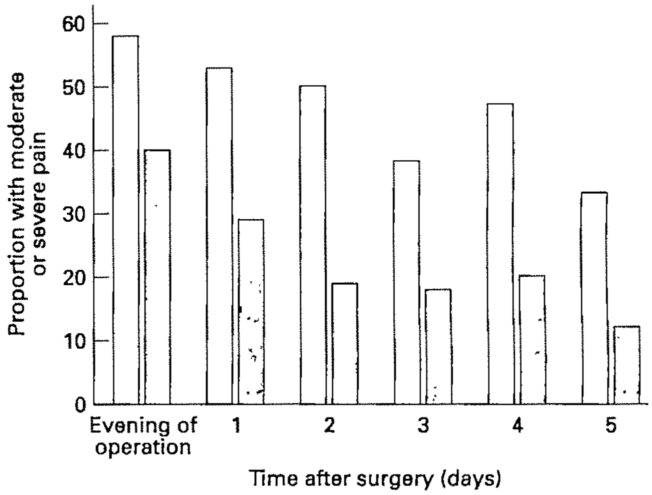

Fig. 1 Proportion of patients with moderate or severe pain following haemorrhoidectomy or pilonidal sinus surgery (□) compared with other procedures (⬚) over the first 5 days after operation

Overall, 79 per cent found day surgery convenient or very convenient and 82 per cent rated the experience good or very good. These proportions were similar for the haemorrhoidectomy/pilonidal sinus group (81 and 83 per cent respectively). If offered a choice for a similar operation in the future, 75 per cent would choose day surgery and even more would prefer a 1-month wait for day surgery over a 6-month wait for inpatient care with an overnight stay.

Conclusion

Day-case coloproctology can be performed safely with minimal impact on primary healthcare services. Pain may be greater after more complex procedures and various techniques have been used to reduce pain after haemorrhoidectomy[1-3]. Despite this, patient tolerance and acceptability remains high. This study emphasizes the need for increased communication with patients, particularly from medical staff. With appropriate explanation and attention to detail, day-case coloproctology may be performed with a high degree of patient satisfaction.

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Combining the strength–duration curve of the external anal sphincter with manometry for the assessment of faecal incontinence

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Background The strength–duration curve of a muscle is thought to be a measure of its innervation. This study was designed to evaluate the ability of the strength–duration curve of the external anal sphincter to discriminate between controls and patients with faecal incontinence.

Methods Forty-three women with faecal incontinence due to sphincter weakness were studied together with 45 age-matched women with no disorders of defaecation. Strength–duration curves of the external anal sphincter and anorectal manometry were recorded for all subjects with the additional measurement of pudendal nerve terminal motor latency in the incontinent group.

Results Logistic regression was performed using resting and voluntary squeeze pressures and current strengths at 28 different pulse durations to develop a predictive equation for incontinence. Only currents at 1 and 6 ms were significant predictors. When anorectal manometry data were included, only the current required to elicit contraction at 1 ms was necessary. The following regression equation can be applied to predict continence in this population with a sensitivity of 95 per cent and a specificity of 100 per cent: $\mathrm{logit}(P) = 4{\cdot}1605 - (0{\cdot}0559 \times \text{squeeze pressure}) - (0{\cdot}1755 \times \text{resting pressure}) + 0{\cdot}8622 I_{1\,\mathrm{ms}}$. A negative value indicates continence.

Conclusion The strength–duration curve, when used in conjunction with anorectal manometry, may have a role in the investigation of faecal incontinence.

Faecal incontinence in women is related to childbirth[1] and is often associated with damage to the nerves that innervate the external anal sphincter (EAS) and the puborectalis[2,3]. This damage can lead to progressive deterioration in the function of the pelvic floor with the onset of symptoms in later life.

History and examination may predict the manometric findings[4] in patients with faecal incontinence. However, there is considerable overlap in the anorectal pressure profile of patients with faecal incontinence and continent subjects[5]. Specialized investigations such as pudendal nerve terminal motor latency (PNTML) and electromyography (EMG) are not universally available to colorectal surgeons[6]. It has been shown in two separate studies that 92 per cent of patients with faecal incontinence have weakness of the EAS[7] and up to 75 per cent have increased PNTML[8].

The strength–duration curve is a measure of the excitability of muscle or nerve tissue and has been used in the assessment of nerve dysfunction[9]. It is a plot of the minimum current required to elicit detectable muscle contraction at a series of square wave pulses of different duration. The hyperbolic nature of this relationship was first described by Lapicque[10] in 1909. The threshold intensity, that just capable of producing a contraction, varies according to the duration of the current: the shorter the duration, the greater the intensity required to achieve the same depolarization. A stimulus of short duration depolarizes only the nerve fibres within the muscle whilst a long duration can stimulate muscle fibres directly[11]. Muscle is less excitable than nerve and requires stimuli of higher intensity. Therefore, denervation of a muscle shifts the strength–duration curve upwards and to the right.

The aim of the study was to assess the ability of this technique to discriminate between continent subjects and faecally incontinent patients.

Patients and methods

The study was approved by the local ethical committees of the hospitals in which studies were performed.

Forty-three women who presented to a specialist clinic with incontinence to stool of normal consistency, which after clinical evaluation was thought to be due to anal sphincter weakness, were studied. Patients were assessed with anorectal manometry, PNTML and strength–duration curve production. Endoanal ultrasonography was not available. Forty-three age- and parity-matched women attending for elective surgery, and with no symptoms of anorectal dysfunction or previous perineal or pelvic surgery, were recruited as controls. Thirty-four had anorectal manometry and 45 had a strength–duration curve production.

Details were recorded for each subject about parity, the type and number of deliveries, the type and number of any surgical procedures to the perineum and pelvis, and details of defaecation function with particular reference to urgency and incontinence.

Anorectal manometry

A closed water-filled system was used to measure the anal pressure profile as described previously[12]. Resting anal pressure and maximum squeeze pressure were obtained using a station pull-through technique.

Pudendal nerve terminal motor latency

PNTML was measured in the 43 patients with faecal incontinence using the method described previously[12,13].

Strength–duration curve production

With the patient in the left lateral position a moistened lint pad was placed between a 15 × 10 cm flat return electrode and the

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left buttock. The stimulus was applied to the EAS complex via a hand-held electrode placed against the subcutaneous part of the sphincter in the 3 o'clock position by an observer. A series of square wave pulses, beginning with long duration and low intensity, were delivered from a direct current pulse generator (Orthotron, Duffield, UK) by an operator who recorded the minimum current required at each pulse duration for a visible contraction of the EAS to be seen by the observer.

A strength–duration curve for the EAS was constructed based on the minimum current (mA) required to elicit a contraction at the following series of pulse durations: 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0·9, 0·8, 0·7, 0·6, 0·5, 0·4, 0·3, 0·2, 0·1 ms.

Eleven patients had two curves produced with reversal of the roles of operator and observer, and 50 had two curves produced by the same operator–observer combination. All patients with faecal incontinence had the test performed by the same operator–observer combination. For the control group the operator was constant but three observers were used. One test was stopped because of patient discomfort.

Table 1 Demographic and obstetric data

	Controls ($n = 45$)	Patients with faecal incontinence ($n = 43$)
Mean(s.d.) age (years)	49(14·8)	48(12)
Parity		
0	7	2
1	6	8
2	14	17
3	10	11
4 or more	6	5
Not known	2	0
Normal deliveries		
0	11	13
1	5	8
2	14	14
3	7	5
4 or more	6	3
Not known	2	0
Forceps delivery	1	21*
Caesarean section	4	4
Hysterectomy	0	12
Prolapse repair	0	14

*$\chi^2 = 22{\cdot}05$, 2 d.f., $P < 0{\cdot}001$

Statistical analysis

All data were entered into a computer database and analysed using SPSS for Windows (SPSS, Chicago, Illinois, USA). Categorical data were analysed with χ^2 tests. The Mann–Whitney *U* test was used to compare squeeze and resting pressures of the two groups. Logistic regression was used to define membership of the two groups with anorectal pressures and strength duration data as the independent variables introduced in a stepwise fashion. $P < 0{\cdot}05$ was considered significant.

Results

The two groups studied were matched for age and parity; however, a significantly higher number of women with faecal incontinence had had forceps deliveries (*Table 1*). There was also a difference in the number of pelvic operations done in this group: 26 of the 43 patients had had either a hysterectomy or prolapse repair.

Mean(s.d.) anal pressure in patients with faecal incontinence at rest (56(28) mmHg) and on squeezing (40(31) mmHg) were significantly lower than those in controls at rest (92(30) mmHg) and on squeezing (85(44) mmHg) ($P < 0{\cdot}0001$, Mann–Whitney *U* test). The strength–duration curves plotted for the two groups showed complete separation (*Fig. 1*).

Logistic regression was performed using resting pressure, current strengths at the 28 pulse durations, and squeeze pressure to develop a predictive equation for faecal incontinence (*Table 2*). The currents at 6 and 1 ms were found to be significant independent predictors of continence. The sensitivity and specificity were 77 and 84 per cent respectively. When logistic regression was performed using resting and squeeze pressure alone, the model had a sensitivity and specificity of 79 and 68 per cent respectively. The best model used resting and squeeze pressures, and strength of the current at 1 ms:

$$\text{logit}(P) = 4{\cdot}1605 - (0{\cdot}0559 \times \text{squeeze pressure}) - (0{\cdot}1755 \times \text{resting pressure}) + 0{\cdot}8622\, I_{1\,\text{ms}}$$

Table 2 Logistic regression models for the discrimination of faecal incontinence using strength–duration curves at 1 and 6 ms and anorectal manometry

						Model		
Inclusion data	Coefficient	SE	*P*	Sensitivity (%)	Specificity (%)	χ^2	d.f.	*P*
Strength–duration data				77	84	53·7	2	<0·0001
6 ms	0·492	0·116	<0·0001					
1 ms	−0·452	0·147	0·0003					
Constant	−2·779	0·822						
Anal pressures				79	68	40·77	2	<0·0001
Resting pressure	−0·0413	0·0119	<0·0001					
Squeeze pressure	−0·0310	0·0092	0·0001					
Constant	5·0772	1·1474						
All data				95	100	87·61	3	<0·0001
1 ms	0·8622	0·3505	<0·0001					
Resting pressure	−0·1755	0·0716	<0·0001					
Squeeze pressure	−0·0559	0·0252	0·0019					
Constant	4·1605	3·1453						

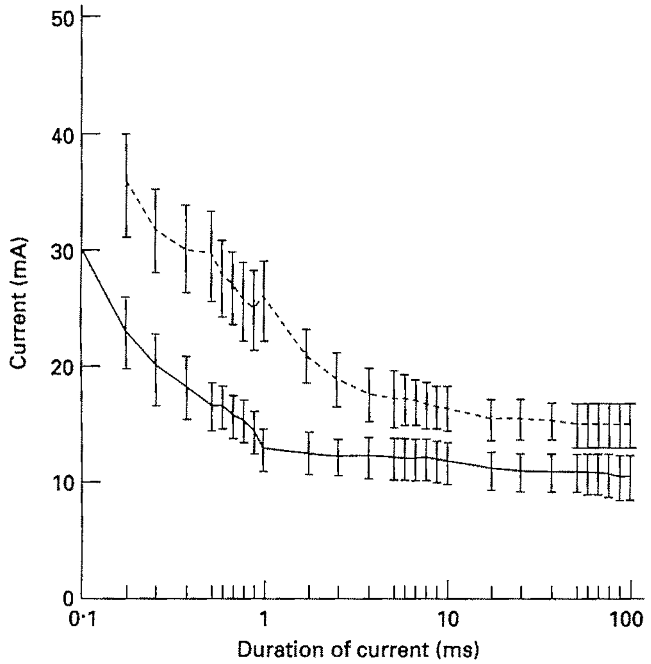

Fig. 1 Strength–duration curves for controls (—) and patients with faecal incontinence (- - -). Data show the minimum current required to elicit a contraction of the external anal sphincter at each current duration (log scale); error bars represent 95 per cent confidence intervals of the mean

$I_{1\mathrm{ms}}$ is the current required to produce a contraction at 1 ms. A negative score indicates normality and a positive score denotes faecal incontinence. This model has a sensitivity of 95 per cent and a specificity of 100 per cent.

PNTML was obtained in 37 of the incontinent patients. In 26, PNTML was greater than 2·1 ms. When correlations were performed between points on the strength–duration curve, the greater of the two PNTML values (PNTML$_{\mathrm{max}}$) and squeeze pressure, no correlation was found. A weak correlation existed between the $I_{1\mathrm{ms}}$ and voluntary squeeze pressure (current at 1 ms = 25·44 − (0·11 × squeeze pressure); $r^2 = 0{\cdot}17$, $P < 0{\cdot}01$). No correlation between PNTML and squeeze pressure was observed in patients with faecal incontinence.

Scattergrams of anorectal pressures, current at 1 ms and logistic regression scores for normal subjects and patients with faecal incontinence were constructed (*Fig. 2*). There was considerable overlap when each investigation was undertaken alone. It can be seen, however, that there is little overlap between the two groups with regard to logistic regression scores, demonstrating the power of discrimination of this combination of investigations.

The repeatability and reproducibility of the strength–duration technique was evaluated in 50 subjects who had two successive curves produced by the same observer, with a precision of 2 per cent when evaluated at pulse durations of 1 and 6 ms. In 11 subjects, two successive strength–duration curves were produced by different observers, with a precision of 10 per cent for the 1- and 6-ms values.

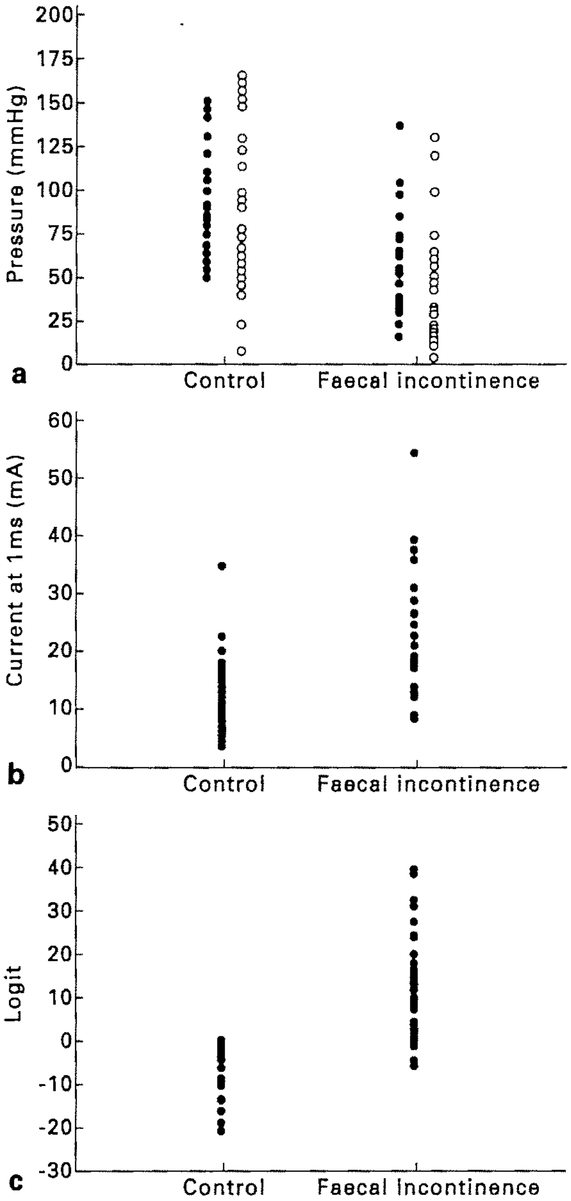

Fig. 2 Scattergrams showing a resting anal pressure (●) and squeeze pressure (○), **b** current strength at 1-ms duration, and **c** logistic regression scores obtained using resting pressure, squeeze pressure and current strength at 1 ms as independent variables

Discussion

This study has shown that, by using $I_{1\mathrm{ms}}$ and $I_{6\mathrm{ms}}$, faecal incontinence can be predicted with a sensitivity of 77 per cent and a specificity of 84 per cent using the logistic regression model. This is an improvement on anorectal pressures alone when, in addition, the specificity is lower than the sensitivity. However, the best model for discrimination of continence was obtained by the combination of anorectal pressure data and $I_{1\mathrm{ms}}$, with 100 per cent specificity and 95 per cent sensitivity.

It is well established that damage to the pudendal nerves during childbirth is the single most important factor in the development of late faecal incontinence[3,14,15]. This may also be associated with a defect in the anal sphincter, particularly if there has been a history of episiotomy or perineal tear during parturition[16]. Nerve damage alone may not be clinically apparent until later life.

Endoanal ultrasonography was not available at the time of this study. It is likely that some of the patients studied had anterior sphincter defects, which influenced sphincter pressures. However, strength–duration curve production should not have been affected. It is known that anterior sphincter repair results are poorer where PNTML is prolonged. The question remains whether the strength–duration curve may be a more sensitive prognostic indicator.

Evidence of neuropathy in the EAS is commonly found in patients with faecal incontinence. Prolongation of PNTML has been noted in 49–52 per cent of patients with incontinence[8,16]. Increased fibre density on single-fibre EMG is a mark of the reinnervation following nerve damage, and was found in 85 per cent of a heterogeneous group of patients with incontinence[17]. The incidence of neuropathy is higher when more than one method of assessing nerve function is used[8]. It is likely that this neuropathy deteriorates with time[18]. However, PNTML may remain normal in patients with faecal incontinence and low squeeze pressures as long as there are surviving fast-conducting nerve fibres. Consequently many studies, including this one, have shown no correlation between squeeze pressure and PNTML.

EMG, PNTML and strength–duration testing are all measures of innervation. Concentric-needle EMG detects muscle action potentials in up to 50 motor units in response to active contraction. It relies on higher function and an intact pathway from cerebral hemisphere to motor endplate. PNTML on the other hand is a measure of the conduction in the last few centimetres of the pudendal nerve. It has been shown previously, in the ulnar nerve, that nerve conduction can be normal despite the supplied muscles exhibiting histological changes of denervation due to a severe incomplete nerve lesion[9].

The strength–duration curve is a measure of the excitability of tissue. As a result of the greater excitability of nerve over muscle, it is able to distinguish degrees of innervation[19]. For muscles with an intact nerve supply, the stimulus produces a muscle contraction as a result of excitation of the intramuscular nerve fibres. If there is abnormality of this nervous tissue due to more proximal nerve damage, the muscle fibres require direct excitation with higher currents and longer pulse durations.

There are several advantages to the technique of strength–duration curve production. It is non-invasive and acceptable to patients. Data were recorded at 28 different pulse durations, and the investigation was abandoned in only one patient owing to discomfort. It takes approximately 2 h to train an observer–operator combination, who need have no previous experience of electrophysiological testing. The equipment is inexpensive and portable, allowing measurement on the ward and in outpatients.

This study of the technique on the EAS has defined a range of normal values. It seems that the whole strength–duration curve is unnecessary to discriminate between the controls and faecally incontinent patients, as $I_{1\text{ms}}$ in conjunction with resting and squeeze pressures gives a highly sensitive and specific result. There remains speculation about the future continence of control patients whose logit value was approaching zero. To establish the clinical value of this technique, further work is necessary to determine the natural history of asymptomatic patients with abnormal strength–duration curves after delivery and how the strength–duration curve varies with other defaecation disorders. In this study only a single strength–duration measurement was taken for each patient but, having found that only the 1- and 6-ms points are significant predictors of incontinence, multiple values at these durations could be used in the future to improve precision. It could be argued that the strength–duration technique is subjective, but the data confirm good concordance of repeated measures by the same observer on the same day. There is considerable temporal variation with whatever technique is used[20].

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Cost-effectiveness in the management of patients with oesophageal cancer

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Background The aim of this study was to assess the relationship between clinical outcome, quality of life and cost for treatment modalities commonly employed in the management of oesophageal carcinoma.

Methods A series of 51 patients diagnosed with oesophageal carcinoma in a 6-month period was used to derive a cost analysis profile for their treatment. All patients underwent quality of life assessment. Patients diagnosed in 1993 and managed in Newcastle upon Tyne were identified from the Northern Cancer Registry and Hospital Episode Statistics. Intervention profiles were documented for a 3-year follow-up period and cost analysis was conducted. A further 51 patients were recruited prospectively for quality-of-life studies.

Results Some 139 individuals were identified retrospectively. Median survival was significantly better in patients treated by resection ($n = 31$; median 20 months) than in those receiving palliative treatments ($n = 108$; median 6 months) ($P < 0{\cdot}0001$). Median cost was significantly greater in individuals who underwent resection (£8070) than for patients subjected to a palliative strategy (radiotherapy £4720, brachytherapy £1790, laser £3540, intubation £2450, no treatment £1390) ($P < 0{\cdot}01$). When considering the median cost per month of life (after treatment) resection (£457) compared favourably with the palliative options (range £342–1125).

Conclusion Surgical resection for oesophageal carcinoma confers greatest benefit in terms of survival. Costs are inherently greater in individuals undergoing resection but, allowing for time, resection is at least as cost-effective as other treatment modalities.

Oesophageal cancer accounts for approximately 5600 deaths annually in England and Wales[1,2]. While the incidence of squamous cell carcinoma remains constant, adenocarcinoma of the oesophagus and gastro-oesophageal junction has the fastest increasing incidence of any solid tumour in Europe and North America today[3]. Despite this, the economic implications of the treatment of oesophageal cancer have received little attention.

There are several treatment options for patients diagnosed with oesophageal cancer. The only hope of cure for these patients is complete surgical resection of the tumour with or without adjuvant or neoadjuvant therapy. Unfortunately, most patients (60–70 per cent) have incurable disease at the time of diagnosis, either because their general physical health prohibits radical treatment or because the disease is too advanced for cure to be a realistic expectation of surgery[4,5]. For these patients several different management approaches can be considered. Appropriate selection of treatment strategy should take account of the cost of therapy. Although clinical effectiveness has been compared between modalities, the cost implications of curative treatment and the various palliative treatment strategies for oesophageal cancer have not been evaluated formally. The aim of this study was to assess the relationship between clinical outcome, quality of life and cost for the modalities most commonly employed in the management of patients with oesophageal carcinoma.

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Patients and methods

One hundred and thirty-nine patients diagnosed with primary oesophageal carcinoma between 1 January and 31 December 1993 were identified from the former Northern Region Cancer Registry and Hospital Episode Statistics. Case notes were retrieved and information regarding the management over a 3-year period (or until death) was recorded on a standardized pro forma. Seven sets of notes were untraceable and, although survival data were available for these individuals (who were known to have had palliative treatment), full assessment could only be conducted for 132 patients.

Fifty-three consecutive patients due to commence treatment for oesophageal cancer at Newcastle General Hospital between 30 September 1996 and 31 March 1997 were approached to take part in the study for quality of life assessment. Fifty-one patients gave their written informed consent to participate. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the OES 24, a disease-specific module undergoing development, were used to evaluate quality of life[6,7]. Questionnaires were completed before treatment commenced and at monthly intervals for 3 months following the date of first treatment. Pretreatment assessment was conducted with an interviewer present while subsequent questionnaires relied on postal responses.

A cost analysis pro forma detailing the intervention profile for each strategy was constructed using clinical information collected from the prospectively recruited cohort of patients. Procedural costs were calculated for endoscopic, radiotherapeutic and surgical interventions (accounting for staff and equipment costs in each case), as well as the cost of outpatient, inpatient and intensive care unit episodes (*Table 1*). To ensure confidence in the resulting cost profile, every effort was made to derive the cost of each management strategy from its component parts; for procedures such as oesophagectomy, the difference in cost between an uncomplicated resection and one requiring prolonged intensive care support is potentially vast. All possible component costs were identified, to ensure that the profile would

Table 1 Summary of procedural costs employed in the cost profile

	Cost (£)
Basic endoscopy	111·16
Additional endoscopic procedures*	
Diagnostic endoscopy (includes histological investigation)	58·07
Endoscopic dilatation†	75·63
Endoscopic endoprosthesis insertion‡	92·95
Intraluminal laser therapy§	102·36
Intracavitary radiotherapy	417·82
Oesophagectomy	
Equipment and histological investigation	865·20
Staff costs (per h)	115·06
External beam radiotherapy (per session)	96·00

*Cost in addition to that for basic endoscopy. †Costing based on the use of guidewire and image intensifier during the procedure; ‡costing based on the use of Wilson–Cook endoprosthesis and introducer; §costings based on the use of a neodymium yttrium–aluminium–garnet carbon dioxide laser

cover any scenario that would be encountered in the retrospective data. Information was compiled from the case notes and the opinions of experienced medical and nursing staff routinely involved in each procedure. Staff costs were calculated by recording the staff requirements (including grade of staff) for and the duration of a given procedure. In determining equipment costs, the current purchase cost, nature of guarantee, service contract and life span was identified in each case. Incremental surcharges were employed to account for intangible costs such as heating, lighting, building maintenance and administration. To minimize uncertainty a risk averse strategy was adopted, such that if there was any doubt with regard to the precise magnitude of a particular variable, the upper margin of estimation would be employed[8]. The resulting cost analysis algorithm was applied to the data acquired from case note review of the retrospective cohort. A total cost of treatment was derived for each patient. As a crude measure of cost-effectiveness, the cost incurred in each case was related to survival from date of diagnosis. By considering the median cost per month survival for each treatment strategy, an incremental cost per unit survival was obtained in a similar manner to that employed by Webb and colleagues[9].

Cost and quality of life were compared between groups by primary treatment allocation using the Mann–Whitney and Kruskal–Wallis tests. Survival curves were produced using the method of Kaplan and Meier, with significance being determined using the log rank test. Statistical significance was attributed when $P < 0·05$.

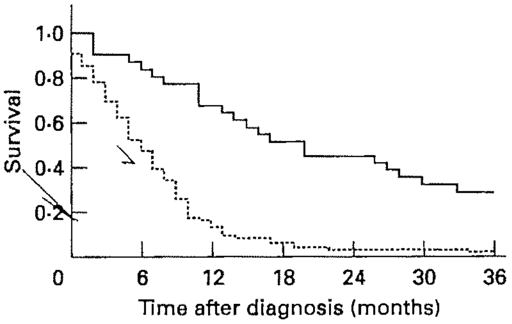
Ethical approval for this study was granted by the Joint Ethics Committee of the Newcastle and North Tyneside Health Authority.

Results

The mean age of the 51 individuals recruited prospectively was 67 (range 48–86) years. Thirty-nine participants were men. Adenocarcinoma was diagnosed histologically in 27 individuals, squamous cell carcinoma in 23 and details of the histological diagnosis were not available in one case. Primary treatment allocation was surgical resection ($n = 17$), external beam radiotherapy ($n = 17$), intracavitary radiotherapy ($n = 6$), chemotherapy ($n = 8$) and endoscopic endoprosthesis insertion ($n = 2$); one individual opted against hospital management. Clinical data from these patients were used to compile the hospital management cost profile for oesophageal carcinoma. Pretreatment assessments were completed for all individuals in the study group. Post-treatment assessments were made with varying degrees of compliance; 20 individuals completed the assessment in full, 13 returned some of the assessment material and 11 did not return any. In addition five individuals died before the end of the first month after treatment and two had not started treatment by the end of the study period. Because of the small number of patients with adequate serial measurements of quality of life, the reliability of comparisons between treatment groups and within treatment groups over time, particularly negative inferences, is limited. Nevertheless, overall there was a trend toward better quality of life among patients undergoing surgical resection compared with other modalities. Specifically, resection conferred significant improvements in reported postoperative dysphagia compared with the palliative modalities. However, this was at the cost of a reduction in reported physical functioning and global health/quality of life scores.

The mean age and gender mix of the 132 patients whose notes were retrieved and studied retrospectively were similar to those of the group recruited prospectively (age 68 (range 44–93) years; 93 men). The histological diagnosis could only be recorded with certainty for 119 patients; there were 58 cases of squamous cell carcinoma, 56 of adenocarcinoma, three of small cell carcinoma and two of 'carcinoma *in situ*'. Patients were grouped according to the primary treatment they received: surgical resection ($n = 31$), external beam radiotherapy ($n = 47$), microselectron ($n = 6$), endoluminal laser therapy ($n = 17$), intubation ($n = 17$) and those receiving no definitive management (other than endoscopy and dilatation) ($n = 14$). In reality, most individuals were managed using more than one therapeutic modality (48 by one, 38 by two, 31 by three and one by four).

Median survival was greater for the group of patients who underwent surgical resection compared with that for individuals who received non-operative palliative treatment or no treatment at all (20 *versus* 6 months; $\chi^2 = 103·80$, 5 d.f., $P < 0·0001$) (*Fig. 1*). Although the majority of the surviving patients at the time of the study



No. at risk							
Resection	31	27	21	16	14	10	9
Radiotherapy	45	29	10	4	1	1	1
Brachytherapy	6	5	2	1	1	1	1
Intubation	16	12	4	1	1	1	0
Laser	15	2	0	0	0	0	0
No treatment	13	0	0	0	0	0	0
No resection	95	49	16	6	3	3	2

Fig. 1 Kaplan–Meier curves comparing survival of patients who underwent resection for oesophageal cancer (———) with that of patients treated without resection (-----). $\chi^2 = 103·80$, 5 d.f., $P < 0·0001$ (log rank test)

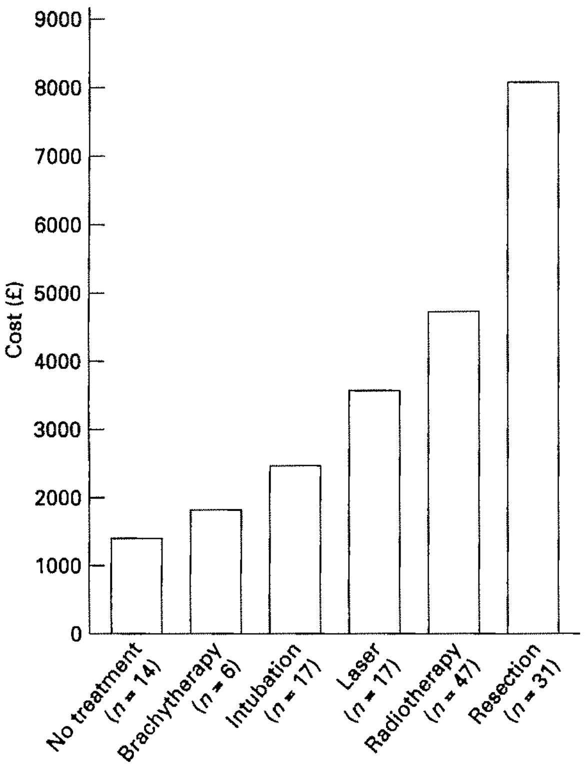


Fig. 2 Median cost of treatment of oesophageal cancer by primary treatment modality employed

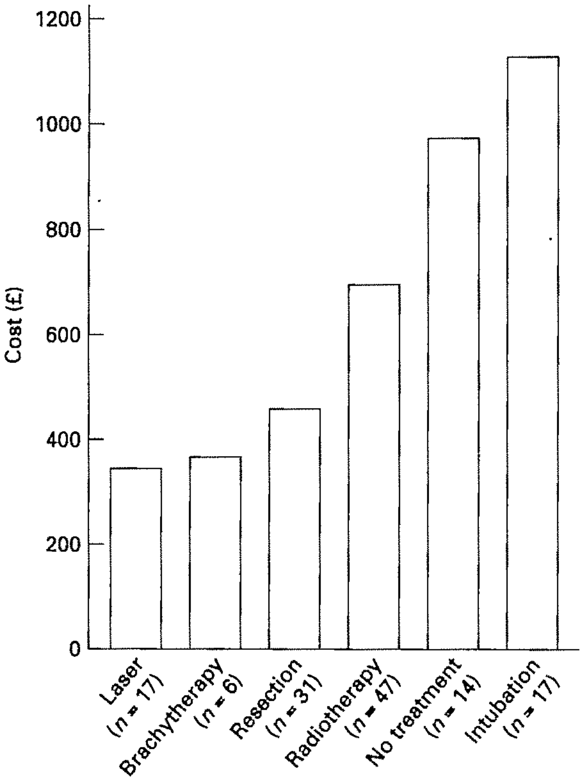


Fig. 3 Median cost of treatment per month of survival after treatment of oesophageal cancer by primary treatment modality employed

had undergone oesophagectomy (nine of 11), one patient receiving external beam radiotherapy and another who underwent intracavitary radiotherapy were among the survivors; both had stage I disease but were unsuitable for or unwilling to undergo radical resection.

The median cost of hospital management over the follow-up period was significantly greater for individuals who underwent surgical resection (£8070 (interquartile range (i.q.r.) £6441–9830)) than for patients subjected to a palliative strategy ($\chi^2 = 44{\cdot}77$, 5 d.f., $P < 0{\cdot}0001$, Kruskal–Wallis test) (*Fig. 2*). The range of costs incurred over the time period studied was also greatest in individuals who underwent resection (minimum £2548, maximum £39 789). Among the range of palliative treatments differences in cost were also significant (external beam radiotherapy £4720 (i.q.r. £3364–6687), brachytherapy £1790 (£1552–7096), laser £3540 (£2531–6341), intubation £2450 (£1647–5550), no treatment £1390 (£1132–2348); $\chi^2 = 20{\cdot}82$, 4 d.f., $P = 0{\cdot}0003$) (*Fig. 2*).

Using survival as a crude marker of effectiveness of treatment, median cost per month of survival was calculated. At £457 per month, resection compared favourably with the least expensive palliative strategies: intracavitary microselectron (£364 per month) and endoluminal laser therapy (£342 per month) (*Fig. 3*).

Discussion

The total of 139 individuals identified for the retrospective study is consistent with the expected incidence in the population studied. A small proportion of incident cases might evade the search methods employed, particularly those who died before hospital referral. Their exclusion from the study introduces a potential bias into the calculation of median cost of management for the group receiving no definitive treatment. The majority of the study population (77 per cent) received palliative management strategies. Fourteen patients did not receive any treatment: eight with very advanced disease or in very poor health and six who died before the allocated treatment could be given. It is important to note the short survival time observed in various individuals who did receive active intervention. This brings into question whether the group receiving no treatment at all should have been larger.

The ability to conduct accurate comparisons of therapeutic cost-effectiveness is required in many fields of medicine. Despite the potentially large costs involved, cost-effectiveness in the treatment of malignant disease and palliative therapy has received little attention. This may be due to the inherent difficulties in performing such studies. Patients with malignant disease are sometimes difficult to recruit and there is a potentially high rate of attrition, particularly among patients receiving palliative therapy[10]. An extremely wide range of response rates is reported in postal surveys of between 10 and 95 per cent. When self-completion questionnaires are administered after an initial interview the response rates can rise to 80 or 90 per cent. The response to recruitment in this study was considerably better than might have been anticipated; only two of 53 patients approached declined to participate. There were no identifiable characteristics in either which differed significantly from those of patients who agreed to take part. There were no distinguishing demographic features that characterized non-respondents or which might have suggested the reasons underlying incomplete or non-response. It may be postulated that response correlated with the stage and prognosis of an individual's disease, but this observation was not supported by the findings of the study.

A second difficulty with studies of this nature is to define 'effectiveness'. The simplest outcome measure is survival since patients receiving palliative treatment for oesophageal cancer are likely to succumb to their disease between 2 and 10 months from diagnosis[11]. Nevertheless overall quality of life represents a more appropriate measure of outcome. Quality of life is not easily measured[12]. The EORTC QLQ-C30 questionnaire is an extensively validated tool which evaluates various domains considered to encompass the theoretical components of 'quality of life'. The questionnaire incorporates a range of physical, emotional and social health issues relevant to a broad range of patients with cancer irrespective of their specific diagnosis and allows the incorporation of a disease-specific module[13–17]. The OES 24 questionnaire contains supplemental questions designed to evaluate specific consequences of oesophageal pathology including dysphagia. Whether improvement in one domain makes up for deterioration in another is a subjective judgement. Persistent decreases in function and increases in symptomatology were reported by the surgical patients throughout the 3-month study period; restitution to the levels seen before surgery may not occur until at least 6 months after resection[18].

Although details relating to procedural interventions have been intensively documented in this study, no attempt has been made to evaluate the contribution of low-cost consumables or to derive community-based costs. It was decided that the amount of time required to document these variables adequately was disproportionate to the value of their inclusion; it is important to maintain a pragmatic approach in what can become an increasingly labour-intensive task. Although it was felt that the derivation of estimated costs for each group was as stringent as might be achieved within the time period of the study, it would have been desirable to validate the resulting data by conducting sensitivity analysis; the lack of such analysis must be considered as the major shortcoming of this aspect of the study[8]. The optimum method for deriving the cost of variables such as operating theatre usage was assessed by examining recent publications to provide substance to the selection of an appropriate strategy. Details of the specific breakdown of cost derivation were nevertheless found to be vague. The derivation of a definitive cost profile for prospective use may also require the differential value of future health benefits to be accounted for (by discounting) if authoritative cost-effectiveness analysis is to be achieved. There is still considerable debate as to the appropriate increment[8].

The range of costs observed for surgical resection is particularly broad. Individuals undergoing oesophagectomy survive longer and are therefore more likely to receive more than one treatment modality. The extremely high management cost of the complications that may occur as a consequence of oesophagectomy is also a significant factor. Undertaking oesophagectomy in specialist centres which can provide all facilities and modalities to minimize complications may have considerable benefits in terms of keeping costs down.

Evaluating cost-effectiveness in a health care setting is fraught with methodological difficulty. Existing approaches provide no satisfactory means of relating financial cost to a holistic measure of health care outcome. When considered in terms of the median cost per month of survival, the high hospital cost incurred by resection compares very favourably with the cost of other treatment modalities; the cost margin between resection and the least expensive palliative strategies is clearly a small price to pay given the significant differences in survival. The values listed for surgical resection, external beam radiotherapy and microselectron are not fixed since there are individuals in each of these groups who are still alive to date. As long as these individuals continue to survive without the need for intervention due to their oesophageal tumour, then the cost per month survival will continue to decrease. This effect will obviously be most marked for the group that underwent resection, since the number of survivors is much larger.

It is interesting to note that the cost per month of endoprosthesis insertion was greater than that for individuals who received no definitive therapy. This should not suggest that endoprosthesis insertion is an ineffective strategy in the management of oesophageal carcinoma. The primary aim of such therapeutic approaches is to palliate symptoms rather than to improve survival. If the cost-effectiveness of such management options is to be evaluated meaningfully, then benefits must be measured in terms of quality of life, not quantity.

Investigation conducted over a much longer time frame would be beneficial. This would enable documentation of the impact of delayed-onset complications such as benign stricture formation or chronic pulmonary damage on an individual's self-assessed quality of life and level of function. Formal assessment of the changes perceived by the patient will provide peer information which can be incorporated into patient education and add a further dimension to the informed selection of management strategy.

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Learning curve for oesophageal cancer surgery

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Background Surgical training and experience are frequently claimed to influence early and late outcome measures. The aim of this study was to examine any improvement in an individual surgeon's performance in one operation over a period of 7 years from initial appointment to date.

Methods Patients undergoing Ivor Lewis subtotal oesophagectomy performed by a single surgeon between April 1990 and December 1996 were identified from a prospectively compiled oesophageal cancer database. Operating time (abdominal, thoracic and 'one-lung time'), blood loss, transfusion requirements (intraoperative and total), extent of lymphadenectomy (number of lymph nodes sampled), intensive treatment unit (ITU) stay, hospital stay, postoperative morbidity and mortality, pathological stage, grade and survival were recorded.

Results The records of 150 patients were identified for analysis. The cohort was split into five groups, each of 30 patients operated on consecutively. Each of the groups was comparable for age, sex, smoking history, preoperative haemoglobin and creatinine levels, weight loss, American Society of Anesthesiologists' grade, and histological stage and grade of disease. Analysis of the variables pertaining to operation revealed a significant improvement with time including reduced single-lung operating time ($P = 0{\cdot}01$), reduced blood loss ($P = 0{\cdot}03$), reduced transfusion requirement ($P < 0{\cdot}0001$), reduced ITU stay ($P < 0{\cdot}0001$), reduced inpatient stay ($P < 0{\cdot}0001$) and an increased yield of lymph nodes ($P < 0{\cdot}0001$).

Conclusion This study showed a continuing improvement in a surgeon's performance over a 7-year period. With the current trend to shorter training periods there is a case for continuing supervision of the 'fully trained' surgeon within highly specialist units.

In the UK there have recently been radical changes in surgical training[1]. Inherent to the argument for this new design of training is that shorter and more structured training will result in better surgeons than those trained by the traditional 'apprenticeship' role. Nevertheless, the shorter period of specialist training raises concerns among trainees and consultants about the adequacy of future specialist appointments. Questions regarding the adequacy of this training and the need for postaccreditation supervision remain unanswered.

There is good evidence that outcome following surgery for colorectal cancer is better if a surgeon performs such operations more frequently[2]. Undoubtedly a surgeon passes through a learning curve for a particular operation. In the cases of complex surgery such as oesophagectomy, there is currently no evidence on which to judge how long such a learning curve is, and how many operations surgeons must perform in order to attain their best results. This has important implications for the length of training and the requirements of postaccreditation supervision.

The aim of this study was to evaluate whether a learning curve for oesophagectomy can be observed in operative and postoperative parameters in the years after appointment of a surgeon and apparent completion of training. The study examined the performance of a single surgeon doing a single operation (the Ivor Lewis subtotal oesophagectomy) over a 7-year period.

Patients and methods

A consecutive series of 150 patients undergoing Ivor Lewis subtotal oesophagectomy by a single surgeon between 1990 and 1996 was studied. Each patient was assigned to one of five groups, A–E, according to the order of operation dates such that group A contained the first to the 30th operated patients, group B cases 31–60, and so on. All preoperative, operative and postoperative details were recorded prospectively on to a pro forma and subsequently transferred to a database (Paradox version 4.5 for DOS; Borland, Scotts Valley, California, USA). Demographic details recorded included sex, age at presentation, alcohol and smoking history. Preoperative haemoglobin and creatinine concentrations, renal function, weight loss, respiratory function (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC)) and American Society of Anesthesiologists' (ASA) grade were also recorded.

Subtotal oesophagectomy was performed as described by Lewis and Tanner[3,4]. Briefly, mobilization of the stomach was performed through an upper midline abdominal incision with the patient supine. The abdominal wound was closed, the patient was turned to left lateral position, and *en bloc* oesophageal resection was performed through a thoracotomy incision via the fifth intercostal space. Oesophagogastric anastomosis was performed with a circular surgical stapler. Two chest drains were placed in the pleural cavity of the right side of the thorax and the wound was closed. This surgical technique was unaltered and there were no significant technical equipment changes throughout the period of study. All operations were performed or supervised by one surgeon (S.M.G.). During the period of the study, six trainees received higher specialist surgical training. In 10 per cent of cases part of the operation was performed by a senior trainee under supervision by the surgeon in charge (S.M.G.).

All patients underwent a standardized preoperative assessment of tumour stage and physical fitness. Anaesthesia was provided by one of two consultant anaesthetists with a special interest in anaesthesia for upper gastrointestinal surgery, using a standardized technique[5]. After operation epidural anaesthesia was not used. Following extubation, diclofenac and opiate patient-controlled analgesia was used. Management thereafter was tailored to the progress of the individual patient. There were

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no significant changes in anaesthetic technique during the period of the study.

Histopathological examination of the resected specimen was performed by one of two experienced gastrointestinal pathologists. Both followed a standardized protocol for dissecting, analysing and reporting tumour stage, grade and lymph node involvement.

The operating surgeon had undergone 10 years of postregistration training together with 1 year of superspecialist surgical training in an oesophageal unit where he had performed 35 oesophagectomies. The anaesthetists were both in post at this unit 5 years before the commencement of this series during which time four to six oesophagectomies were performed each year by another surgeon.

Markers of performance

Operative parameters taken as markers of surgical performance included total operating time, single lung ventilation time, incidence of positive resection margins and number of lymph nodes resected. 'Postoperative' parameters recorded included total blood loss, total blood transfusion requirement, length of stay in the ITU, total hospital stay, the incidence of major and minor complications, inhospital mortality and overall survival.

Statistical analysis

Statistical comparisons for continuous data were made with the Kruskal–Wallis test, ordinal data with the χ^2 test and survival differences with the log rank test, with survival curves constructed according to the method of Kaplan and Meier. All analyses were performed using the Statistical Package for the Social Sciences software (SPSS, Chicago, Illinois, USA). $P < 0{\cdot}05$ was considered significant.

Results

The five sets of patients were similar with respect to preoperative factors and stage of tumour at diagnosis. The mean(s.d.) age of the group as a whole was 62·5(0·7) years, with a sex distribution of 115 men and 35 women. The majority of patients (60 per cent) were ASA grade II, 27 per cent grade I and 12 per cent grade III. Forty-one per cent were smokers at the time of surgery. Comparing the stage of disease, 17 per cent of cases were stage I, 39 per cent stage II and 44 per cent stage III. Simple measures of pulmonary function (FEV_1/FVC) showed a non-significant tendency for the later series to include patients with poorer respiratory function. There was a significant trend towards an increasing proportion of adenocarcinoma to squamous carcinoma (group A, 15:15 *versus* group E, 4:26; $P = 0{\cdot}017$).

Although total operating time and abdominal operating time were not significantly different between groups, single-lung ventilation time was significantly reduced in the later series of patients (*Fig. 1*). Blood loss and transfusion requirement were both reduced in the later series of patients (*Fig. 2*). ITU stay and total hospital stay both showed differences between groups of patients, with a tendency for shorter stay in the patients operated on more recently (*Fig. 3*).

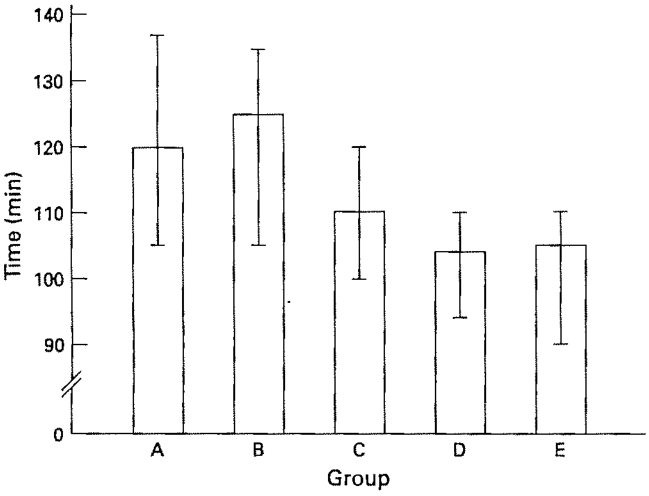


Fig. 1 Median (interquartile range) of one-lung operating time (i.e. duration of the thoracic part of the Ivor Lewis oesophagectomy). Patients were in groups A–E where group A comprised the first 30 cases in the series and group E the last 30. $\chi^2 = 12{\cdot}54$, 4 d.f., $P = 0{\cdot}014$

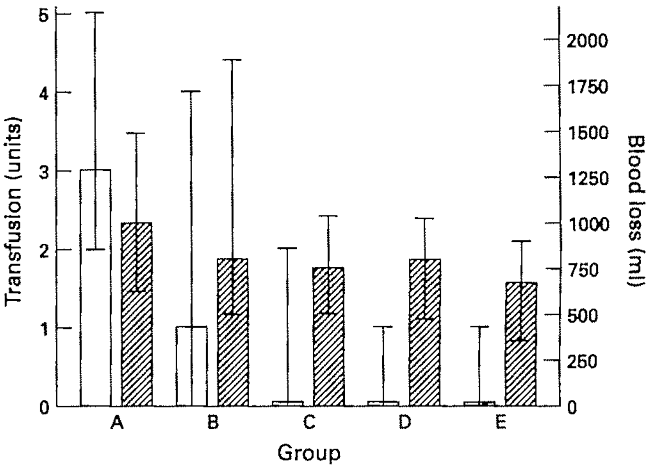


Fig. 2 Median (interquartile range) of intraoperative blood loss (▨) ($\chi^2 = 10{\cdot}74$, 4 d.f., $P = 0{\cdot}03$) and blood transfusion requirements (☐) ($\chi^2 = 32{\cdot}75$, 4 d.f., $P < 0{\cdot}0001$), comparing groups A–E of patients operated on sequentially. The number of patients receiving no transfusion were 10, 12, 18, 20, 21 for groups A–E respectively

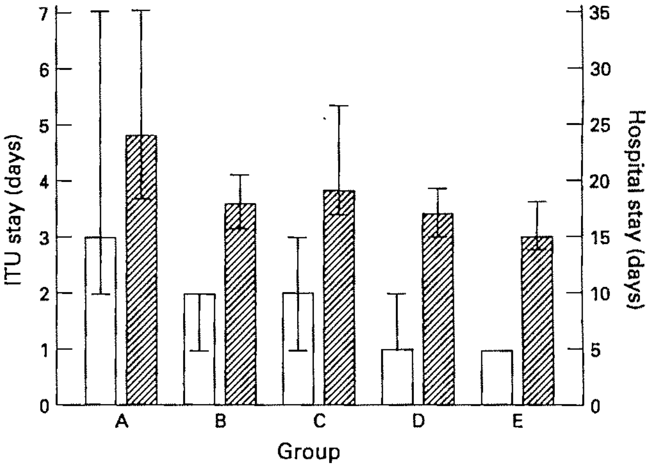


Fig. 3 Median (interquartile range) of the number of days in the intensive treatment unit following surgery (☐) ($\chi^2 = 30{\cdot}95$, 4 d.f., $P < 0{\cdot}0001$) and total hospital stay (▨) ($\chi^2 = 35{\cdot}68$, 4 d.f., $P < 0{\cdot}0001$), comparing groups A–E of patients operated on sequentially

Table 1 Comparison of morbidity, mortality and incomplete resection margins between groups of patients

	Case grouping					
	A	B	C	D	E	P*
Minor complications	10	12	9	8	6	0·53
Major complications	7	8	7	6	4	0·77
Positive resection margins	2	0	1	3	3	0·23
Inhospital death	2	2	0	1	1	0·32

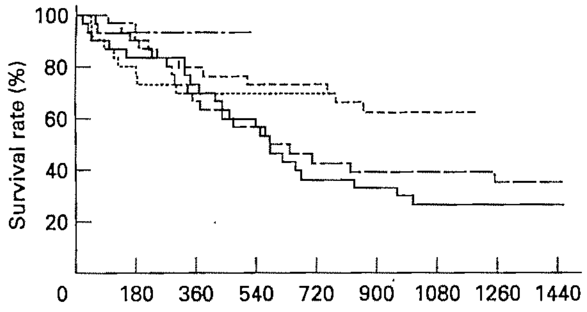
*χ^2 test

The number of lymph nodes harvested was also different between groups, with an increased yield from the later series of patients. The median (interquartile range) lymph node yield in the first 30 cases was 9 (6–11), compared with 15 (9·5–20) and 15·5 (12–20) in groups D and E respectively ($\chi^2 = 29{\cdot}5$, 4 d.f.; $P < 0{\cdot}0001$). There was no significant difference in the incidence of positive resection margins, 30-day or hospital mortality, or in the incidence of major and minor complications although the numbers of each were small (*Table 1*).

Comparison of survival between groups was heavily influenced and potentially biased by the intrinsically different periods of follow-up for each group and by possible stage migration. Nevertheless, survival curves show a survival benefit for patients operated on more recently ($P < 0{\cdot}01$) (*Fig. 4*).

Discussion

The results of this study illustrate the learning curve of one surgeon for one operation: the Lewis–Tanner subtotal oesophagectomy. It confirms that there is an improvement in several important outcome measures which might be regarded as 'performance indicators'. The 'learning curve' drawn from several perioperative indices (operating time, blood loss, ITU stay and lymph node yield) suggests that the surgeon continued to improve for a considerable period of time after apparently completing training.



No. at risk

	0	180	360	540	720	900	1080	1260	1440
Group A	30	25	22	17	11	10	8	8	8
Group B	30	27	20	17	12	11	11	9	6
Group C	30	27	24	22	22	13	4	0	0
Group D	30	22	20	16	4	0	0	0	0
Group E	30	28	19	0	0	0	0	0	0

Fig. 4 Kaplan–Meier plots comparing the survival of groups of patients operated on sequentially ($\chi^2 = 13{\cdot}95$, 4 d.f., $P = 0{\cdot}0075$, log rank test). Life-table analysis of patients 'at risk' at each 6-month interval is displayed below

The concept of the surgical 'learning curve' is often discussed and assumptions regarding the time or number of operations required to reach a plateau on this curve are often made both in respect to adequacy of training and standardization of clinical research. For laparoscopic techniques such as laparoscopic appendicectomy and laparoscopic treatment of ectopic pregnancy, the learning curve has been shown to be short and steep[6,7]. A large Scottish multicentre study demonstrated that the incidence of major bile duct injury following laparoscopic cholecystectomy peaked at 3 years' experience and then began to fall[8]. For more complex surgery, a study of outcome following acoustic neuroma surgery found that a newly formed, but fully trained, team took more than 60 procedures to reach a similar standard to that of more established colleagues[9]. The learning curve for an individual, fully accredited surgeon performing D_2 gastrectomy has been shown to reach a plateau at 15 to 25 cases when the surgeon had performed only two before the study[10]. Watson *et al.*[11] published data relating to the learning curve for laparoscopic fundoplication and found a significantly higher complication rate in the first 20 cases.

Matthews and co-workers[12] have shown, from a retrospective survey of resections for oesophageal cancer, that a considerable improvement in outcome can be demonstrated when surgeons perform six or more oesophageal resections annually. Similar work from Denmark suggests that this complex surgery should be restricted to centres performing at least 20 cases each year[13]. Steele[2] demonstrated a significant improvement in outcome in colorectal cancer surgery with experience. As well as experience, subspecialist training appears to have an independent effect on outcome in colorectal cancer treatment. Improved local recurrence and disease-specific survival rates have been found amongst patients undergoing abdominoperineal resection by surgeons who had undergone subspecialist training[14].

As well as increased operative experience there are other factors that may confound the interpretation of the 'surgeon's' learning curve. In this study there was an increase in the proportion of adenocarcinomas. Although this is unlikely to affect the results reported significantly, it is conceivable that it is a factor that may influence survival, presentation and blood loss during surgery because of the more distal position of such tumours. Furthermore, increased specialization of a surgeon leads to an increase in expertise of an entire team. This is inseparable from the surgeon's personal results. The investigative departments, ward, theatre and ITU staff become more experienced, expert and consistent. Together with other health professionals, including specialist nurses and physiotherapists, they all undoubtedly contribute to the reduced operating time and lower ITU and inpatient stay. The experience and expertise of anaesthetic colleagues has improved in parallel with that of the surgeons and also contributes to a reduced ITU stay, and low perioperative morbidity and mortality rates. Although there was no significant technical change in anaesthetic practice, operative and postoperative care became more standardized with the experience of the unit as a whole. In addition, improvements in histopathological assessments have contributed to the improvement in lymph node yield. Thus, the learning curve described may not simply represent that of an individual surgeon but, more, the learning curve of an evolving specialist centre in which the surgeon has a pivotal role. It may be that, having laid the foundations of a specialist centre, future appointments will attain their optimal performance at a more rapid rate. A prospective audit is in progress to address this question.

A solution to the problem of inequality of experience and hence performance may be to structure the postaccreditation period. This may make the case for concentration of the management of certain disorders to specialist centres and the appointment of a 'mentor' to the newly trained surgeon. This would allow the continued education of the new appointee within the consultant grade. In this way a consultant newly appointed to subspeciality practice would have access to supervision by an experienced colleague for advice and rational allocation of cases between the new appointee and more experienced colleagues. This would, for example, allow straightforward problems to be managed by the junior colleague or operations to be performed jointly by both experienced and junior consultants until such time as the learning curve of the junior colleague reached a plateau. The point at which a clinician is on a learning curve could be readily determined by careful prospective computerized audit of operative indices such as those used in this study. It may be that such a system would better tailor postaccreditation supervision to the need of the surgeon as opposed to a fixed period or fixed number of cases, such as that offered by preaccreditation training.

In conclusion, this study reveals a continuing improvement in overall performance for the outcome of oesophagectomy over a 7-year period following appointment to a consultant post. The changes due to surgical performance are inseparable from those due to improvements in anaesthesia, ITU care and pathological expertise associated with the increased specialization of the unit. With shorter training periods there is a case for continuing supervision of the 'fully trained' surgeon within such specialist units.

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Detection of response to chemotherapy using positron emission tomography in patients with oesophageal and gastric cancer

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Background The aim of the study was to determine whether 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) could detect response to chemotherapy in patients with oesophageal and gastric cancer.

Methods Fourteen patients underwent imaging before and after chemotherapy using FDG-PET. Computed tomography (CT), dysphagia scores and weight changes were used for comparison of evidence of response. Tumour to liver ratios (TLRs) and influx constants for FDG (K) were used for quantification purposes.

Results Thirteen of 14 lesions were successfully imaged before therapy. Changes were seen in all follow-up scans, ranging from a complete response to a 15 per cent increase in tumour FDG uptake. Response was demonstrated by CT in four patients; all four had large reductions in FDG uptake after chemotherapy. Two patients with an increase in FDG uptake reported no improvement in dysphagia and continued to lose weight during therapy.

Conclusion Changes in tumour FDG uptake were seen in all tumours after chemotherapy. FDG-PET may have a role to play in the assessment of patients with upper gastrointestinal malignancy receiving chemotherapy.

Despite significant reductions in the operative mortality rate for patients with oesophageal cancer there has been little improvement in long-term survival in the past three decades[1,2]. Neoadjuvant chemotherapy has the potential to improve survival but response rates in published series are disappointing at approximately 50 per cent[3-7]. Early detection of tumour response to antineoplastic therapy may improve the value of such an approach by allowing continuation of treatment in those likely to benefit while preventing the administration of ineffective and potentially harmful therapy in non-responders. Unfortunately, using conventional imaging modalities the detection of response is often unreliable and is reliant on a change in anatomical appearance; the reduction in tumour size must be great to be detected, often occurring late in the natural pathway of response[8-12].

Positron emission tomography (PET) is unique in its ability to visualize metabolic activity within tissue *in vivo*. The increased glycolytic activity within tumour tissue allows visualization with the positron-emitting glucose analogue 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)[13,14]. FDG uptake into cells is along the same pathway as glucose but, following phosphorylation, it remains trapped intracellularly, enabling detection with PET.

In vitro and animal studies demonstrate a reduction in tumour FDG uptake after chemotherapy and radiotherapy[15,16]. FDG-PET has also been studied as an indicator of response to chemotherapy in a variety of human tumours[17-27]. The aim of this study was to assess the role of FDG-PET in the detection of response to chemotherapy in patients with oesophageal and gastric cancer.

Patients and methods

Fourteen patients with oesophageal or gastric cancer undergoing combination chemotherapy were entered into the study, which was approved by the Joint Ethical Committee of Grampian Health Board and the University of Aberdeen. Ten of the 14 patients were entered into studies of neoadjuvant chemotherapy and four received palliative cisplatin and 5-fluorouracil with or without epirubicin. Patients underwent FDG-PET studies before the first cycle of chemotherapy and after two or three cycles (8–13 weeks). Computed tomography (CT) was performed within 1 week of PET. Evidence of clinical response was determined by changes in weight and dysphagia scores[28] between the first and second PET examinations.

Imaging

PET studies were performed at the University of Aberdeen PET Unit. Pharmaceutical grade FDG was manufactured by an on-site cyclotron. All patients received a 5-mCi (185 MBq) bolus of FDG intravenously. Patients fasted for 12 h and plasma glucose levels were recorded. Scans were performed on a Siemens ECAT EXACT 31 scanner (Erlangen, Germany). In six patients two contiguous beds were imaged for 10 min per bed. Imaging commenced 45 min after injection of FDG. In eight patients dynamic emission scans were started immediately after injection of FDG with a total dynamic imaging time of 50 min. Images were reconstructed using a ramp filter with a Hanning window (cut-off at the Nyquist frequency).

Contrast CT was performed on an IGE CT Pace (Milwaukee, Wisconsin, USA). Contiguous 10-mm sections were taken from the lung apices to the inferior margin of the liver. Intravenous contrast (Iohexol 350 mg iodine per ml; Nycomed, Birmingham,

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UK) was given as an initial bolus followed by an infusion. Oral contrast (400 ml, 3 per cent Gastrografin; Schering Health Care, Burgess Hill, UK) was given before scanning.

Quantification

To allow comparison of images before and after chemotherapy, FDG uptake by the tumour was quantified. In all patients semiquantitative analysis of images was obtained by the calculation of a tumour to liver ratio (TLR) from 10-min static images obtained 35–45 min after injection of FDG. The image was digitalized into regions measuring $3\times3\times3$ mm, termed voxels. For calculation of the TLR the maximal voxel activity within the tumour was divided by the mean activity within a region of interest of approximately 90 voxels within the liver.

Additional quantification was obtained by calculation of the influx constant for FDG (K) in eight patients (K is the steady-state rate of FDG flux from plasma into tumour divided by the plasma concentration of FDG) using the graphical 'Patlak' method[29] on dynamic images and based on the three-compartment model described by Sokoloff *et al.*[30] and Phelps *et al.*[31]. Correlations between the two techniques were assessed by Pearson bivariate correlation. The arterial blood–time activity curve was obtained directly from the reconstructed images using a region of interest (ROI) placed over either the left ventricle or descending aorta. Arterialized venous blood samples were taken during scanning. Activity within the samples was checked against the activity on the ROI curve at the various time points. The Pearson correlation coefficient was greater than 0·9 for each patient. CT images were assessed for evidence of response using previously reported techniques[32]. The images were reported by two radiologists unaware of the PET results.

Results

Three patients had stage II disease, ten had stage III–IV and one had recurrent disease. Mean age was 61 (range 43–77) years. There were two squamous cell carcinomas affecting the middle third of the oesophagus and 12 adenocarcinomas. Twelve of 13 primary lesions showed a high uptake of FDG. TLRs before chemotherapy ranged from 1·46 to 5·58. The primary tumour was not detected before chemotherapy using PET in a patient with linitis plastica and a small tumour plaque on the greater curvature of the stomach. Metastatic disease was detected in two patients. No relationship existed between tumour type, differentiation or stage, and TLR.

A change in TLR was seen in all 13 patients (median reduction 22 per cent, range from complete response to 15 per cent increase). Nine lesions in six patients were quantified using K values in addition to TLR. The correlation coefficient between the two methods was 0·87 ($P<0{\cdot}01$, one-tailed test).

In six patients with a greater than 30 per cent reduction in TLR after chemotherapy, four also had a partial response detected on CT. Three of these patients had no dysphagia throughout treatment, with the other three reporting improvement. Two of these patients had weight gain; the remaining four had minimal or no change. The liver metastases visualized in one of these patients showed reductions in FDG uptake, similar to that in the primary tumour (*Fig. 1*).

Two patients had increased TLR at follow-up. CT showed no evidence of response. Both reported no improvement in dysphagia scores and both lost weight (*Fig. 2*).

Five patients had reductions in TLR of between 0 and 30 per cent. None of these patients had CT evidence of response. Changes in weight ranged from a 10-kg increase to a 5-kg decrease. Three had improvement in dysphagia scores.

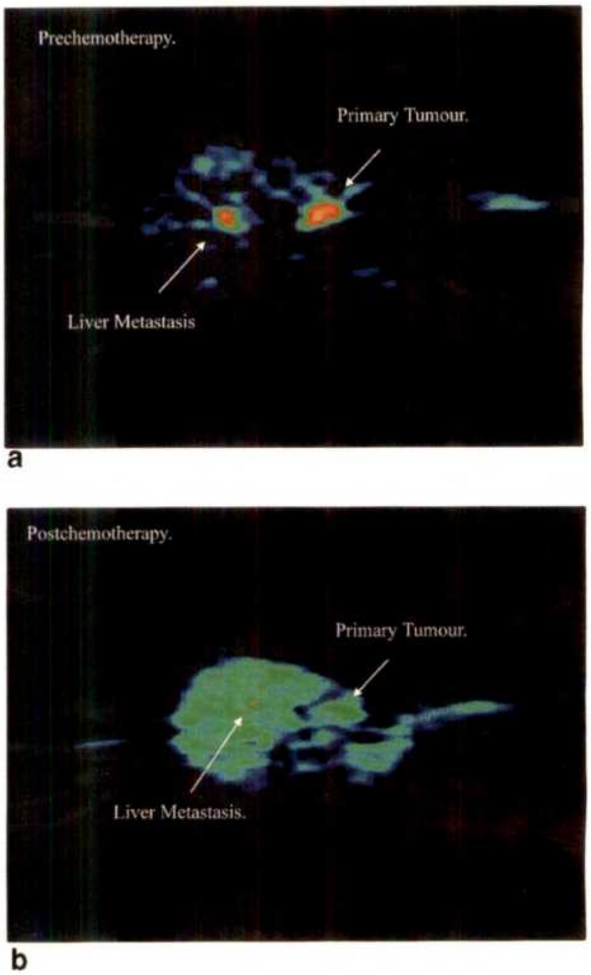

Fig. 1 Positron emission tomograms **a** before and **b** after chemotherapy of a patient with adenocarcinoma affecting the oesophagogastric junction with liver metastases. After chemotherapy the tumour to liver ratio of the primary tumour has reduced by 68 per cent, with a similar reduction in liver lesions

Twelve-month follow-up data are available for six patients who underwent resection. All had node-positive disease on histological examination. The shortest survival was in a patient with increased TLR after chemotherapy. Two patients with 36 and 54 per cent reductions in TLR are alive and disease-free at 24 and 15 months respectively.

Discussion

PET has not been applied widely in the assessment of upper gastrointestinal malignancy. Previous studies have demonstrated PET to be reliable in the detection of patients with oesophageal and gastric cancer[32–40]. However, its usefulness as a staging investigation remains unclear and PET was not used for staging purposes in this study[39,40]. The resolution of currently available PET systems means that small locoregional involved lymph nodes are difficult to detect[33,39]. To date no published study has reported the use of PET as an indicator of

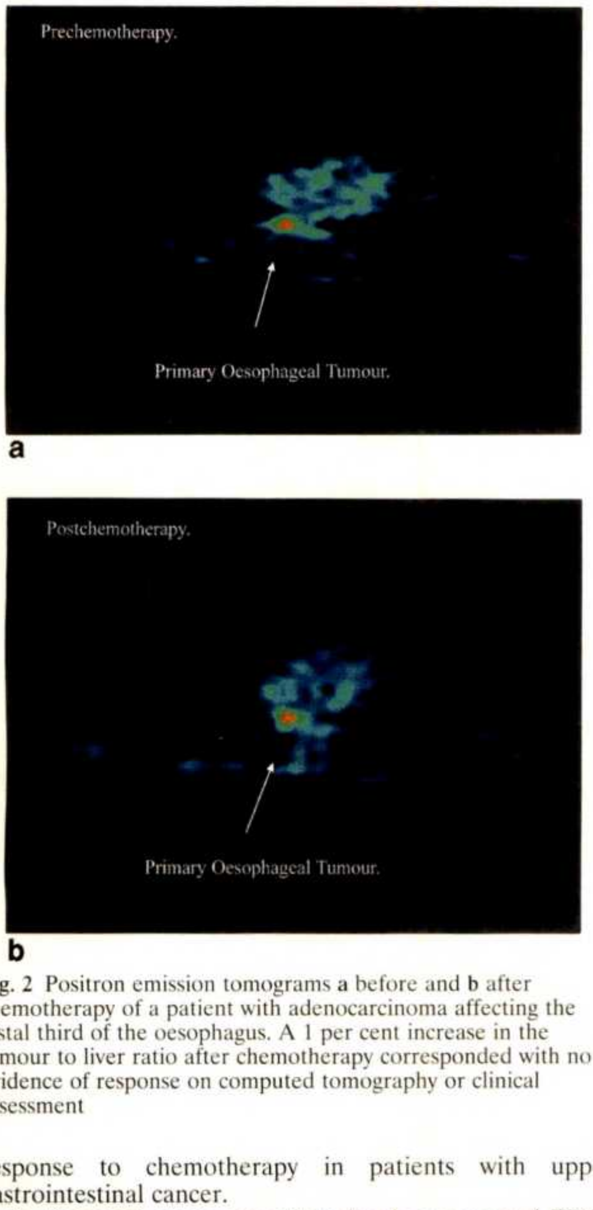

Fig. 2 Positron emission tomograms **a** before and **b** after chemotherapy of a patient with adenocarcinoma affecting the distal third of the oesophagus. A 1 per cent increase in the tumour to liver ratio after chemotherapy corresponded with no evidence of response on computed tomography or clinical assessment

response to chemotherapy in patients with upper gastrointestinal cancer.

As discussed above several studies have assessed FDG-PET as an indicator of tumour response to chemotherapy[17–27]. The majority of studies have small patient numbers and a variety of methods has been used for quantification to allow comparison of images. Semiquantitative analysis can be achieved by calculation of region of interest ratios using liver, brain or muscle for comparison. The mean activity within liver was used for calculation of region of interest ratios (TLRs) in the present study. The use of maximum voxel values within the tumour allows comparison of the most metabolically active tissue. True quantitative measurements were obtained from dynamic images in seven patients by the calculation of the influx constant for FDG (K). This method is more complex than the calculation of TLR and involves longer scanning times for the patient. Good correlation existed between results calculated using both methods and therefore TRL was used to compare images before and after chemotherapy.

A wide range of changes in tumour FDG uptake after chemotherapy was demonstrated. A reduction of more than 30 per cent in activity was seen in six patients but CT demonstrated evidence of response in only four of these cases. It is unclear whether this represents false positives for PET or false negatives for CT. However, early clinical data are in keeping with response in these patients. In patients with increased FDG uptake there was agreement of non-response among clinical assessment, CT and PET. However, in patients with less than 30 per cent reduction in activity it is not clear whether these reductions represent true responses or otherwise and it remains to be determined which level of reduction in activity is a true indicator of response. Larger patient numbers and longer periods of follow-up are needed to determine the clinical and prognostic relevance of these smaller changes detected on PET.

In conclusion, FDG-PET is reliable in the detection of upper gastrointestinal malignancy and demonstrates definite changes in tumour FDG uptake in all tumours imaged before and after chemotherapy. This may enable the detection of response to neoadjuvant chemotherapy and allow better patient selection for continued treatment. Good correlation existed between results calculated using semiquantitative and quantitative analysis. In addition the finding of prolonged survival in a patient with advanced disease who had a large reduction in FDG uptake after therapy indicates that PET may also play a role in the monitoring of treatment in patients receiving palliative chemotherapy.

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Scanning laser Doppler flowmetry and intraluminal recirculating gas tonometry in the assessment of gastric and jejunal perfusion during oesophageal resection

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Background The ability of the new techniques of scanning laser Doppler flowmetry and recirculating gas tonometry to measure changes in gastric serosal and mucosal blood flow respectively during oesophageal resection was assessed.

Methods Changes in regional and total gastric blood flow were assessed in 16 patients undergoing oesophagectomy at three stages of the procedure. Laser Doppler images were analysed and perfusion expressed as mean perfusion units. Tonometric measurements of gastric and jejunal intramucosal pH (pH$_i$) were made synchronously.

Results There were significant falls in gastric perfusion measured with scanning laser Doppler flowmetry in all subjects between each measurement. Mean perfusion of the stomach fell 41 per cent after mobilization. There was a gradient of reduced perfusion between the antrum (mean fall 25 per cent) and the area used for the anastomosis in the fundus (mean fall 55 per cent). Before mobilization mean gastric and jejunal pH$_i$ were 7·37 and 7·46 respectively. These fell to 7·18 and 7·37 respectively after mobilization and to 7·29 and 7·38 after anastomosis.

Conclusion These new techniques could be employed at operation, appear to overcome the limitations of single-point laser Doppler flowmetry and saline tonometry, and have measured significant changes in gastric perfusion. They may have widespread clinical application.

Anastomotic leak following oesophagectomy is a significant cause of death. Ischaemia at the anastomotic site is thought to be an important aetiological factor. Measurement of tissue blood flow in the gastric serosa–muscularis propria and mucosa during operation may enable surgeons to identify patients at risk from this complication.

Single-point laser Doppler flowmetry was first described in 1972[1] and has been used to measure perfusion in gastrointestinal tissue including the stomach. The method relies on the measurement of Doppler frequency shifts in laser light reflected from moving red blood cells and has been validated against other methods of measuring tissue blood flow including hydrogen clearance[2], radioactive microsphere distribution[3], radioactive isotope washout[4], optical plethysmography[5] and electromagnetic flow probe measurement[6]. However, there are several methodological problems associated with the method that have handicapped its use during operation.

Scanning laser Doppler flowmetry (SLDF) is a new development of the technique[7,8]. A laser beam scans over a predetermined area and reflected light is collected by a remote mirror assembly. Thousands of individual measurements of tissue perfusion are made and converted into a colour image with different levels of perfusion represented by different colours. The associated software allows calculation of mean perfusion within areas outlined on the image.

Silicone balloon tonometry[9] allows the measurement of intramucosal pH (pH$_i$) within a number of hollow viscera including the stomach. Mucosal hyperfusion and hypoxia results in a reduced pH$_i$[10,11] and the technique has been used in the assessment of gastric and sigmoid pH$_i$ during, and subsequent to, cardiac[12], aortic[13] and oesophageal[14] surgery. However, intraoperative application of this method has been handicapped by the long time required for equilibration of carbon dioxide within the organ being assessed and the liquid in the tonometer balloon[15]. Recirculating gas tonometry (RGT) is a recent development and allows far more rapid equilibration[15,16].

This study assessed the ability of SLDF to measure changes in gastric serosal and muscularis perfusion, and RGT changes in mucosal pH$_i$ consequent to gastric mobilization in 16 patients undergoing oesophagectomy.

Patients and methods

Sixteen adult patients were studied (14 men; median age 60 (range 44–78) years). All had oesophageal cancer and none had previously undergone any oesophageal or gastric surgery. Anaesthesia was induced and maintained with propofol (8–12 μg per kg per h) and fentanyl (to a total of approximately 30 μg per kg). A gastric tonometer (Tonometrics Division, Instrumentarium Corporation, Helsinki, Finland) was introduced into the stomach and the balloon positioned within the fundus. The tonometer was connected to a Tonocap recirculating gas analyser (Datex-Engstrom Division, Instrumentarium Corporation) which was calibrated according to the manufacturer's instructions. After a laparotomy had been performed a sigmoid tonometer was placed alongside a 10-Fr Foley jejunostomy feeding tube 20 cm from the duodenojejunal flexure. Both tonometers were then automatically primed by the Tonocaps. After an equilibration period of at least 11 min, measurements of intragastric and jejunal partial pressure of carbon dioxide (P_{CO_2}) were made. Arterial samples were taken as the tonometer balloons' contents were being sampled by the Tonocaps and

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Table 1 Regional intraoperative gastric perfusion calculated from laser Doppler scans

	Before mobilization	After mobilization	Fall (%)	P^*	Gastric tube	Fall (%)	P^*
Entire stomach	530(113)	313(114)	41	0·0005	256(133)	52	0·14
Anastomosis site	519(100)	234(82)	55	0·0004	197(112)	62	0·23
Body	510(102)	319(123)	37	0·0005	292(124)	43	0·33
Antrum	526(104)	394(120)	25	0·0005	—	—	—

Values are mean(s.d.) perfusion units. The anastomosis site, body and antral measurements were calculated from 1-cm^2 regions of interest in each of these areas. *Wilcoxon signed rank test

arterial P_{CO_2}, pH and bicarbonate were measured in a standard blood gas analyser (Instrumentation Laboratories IL-1420, Warrington, UK). By entering these values into the Tonocaps the gastric and jejunal pH$_i$ were automatically calculated.

While the tonometers were equilibrating, a laser scan of the stomach was made (Laser Doppler Imager; Moore Instruments, Axminster, UK). The scanner was positioned 32 cm above the patient and the scan area defined using a portable notebook computer on which specially designed software had been installed. This distance was employed as it was found to be the closest at which the whole stomach could be included within a single scan. Standard lighting was maintained and on instruction the laser beam (2 mW helium neon 633 nm) was automatically scanned over the anterior surface of the stomach in a rasta pattern. There was no contact with the patient or the sterile operative field. Each scan took approximately 4 min and contained up to 65 000 individual measurements or pixels of flow (perfusion units; PUs) which were converted into a colour perfusion image map. Subsequently the entire anterior surface of the stomach was outlined on the black and white photographic image produced by the laser at the same time as the perfusion map, and the mean perfusion within this area was recorded as total gastric flow.

In addition, three regions of interest were defined on the laser images. These were each of 1 cm^2 in the gastric antrum, corpus and at the proposed anastomosis site in the fundus. Each contained up to 1750 individual pixels and the mean perfusion within each of these was recorded. Following gastric mobilization and division of left gastric, left gastroepiploic and short gastric vessels the laser Doppler and tonometric measurements were repeated. A final laser scan was made after formation of the gastric tube; mean perfusion was measured at the anastomosis site and in the body, at the site of previous measurements. Final pH$_i$ measurements were recorded on completion of the operation, although the laser Doppler measurements were not repeated at this stage as visualization of the anastomosis site by the scanner was not satisfactory.

All patients underwent a water-soluble contrast swallow 7 days after operation, unless they had developed a clinical leak requiring reoperation in the interim. All were seen in the outpatient clinic for a minimum of 3 months following surgery, and dysphagia was investigated endoscopically with anastomotic biopsy. The results were analysed statistically using the Wilcoxon signed rank test and Pearson correlation.

Results

There were no significant differences in pulse rate, mean arterial pressure or central venous pressure between the three measurement points ($P>0·05$ in all cases). There was, however, a significant fall in haemoglobin concentration between the start of the operation and following gastric mobilization ($P=0·009$). There were three anastomotic leaks, none of which was fatal. Two were proven radiologically; the third patient was returned to theatre and the anastomosis repaired and drained. Another patient died from multiple organ dysfunction, but at autopsy there was no evidence of anastomotic failure. Two benign anastomotic strictures developed within 3 months of surgery.

Before gastric mobilization the laser Doppler imager recorded homogeneous levels of perfusion throughout the stomach and there were no significant differences between perfusion in the three regions of interest ($P>0·5$ in all cases) (*Table 1*). There were large falls in perfusion detected in all parts of the stomach following mobilization (*Figs 1* and *2*). Overall, there was a 41 per cent reduction in mean gastric perfusion from 530 to 313 PUs. The greatest reductions in blood flow were seen in the fundus

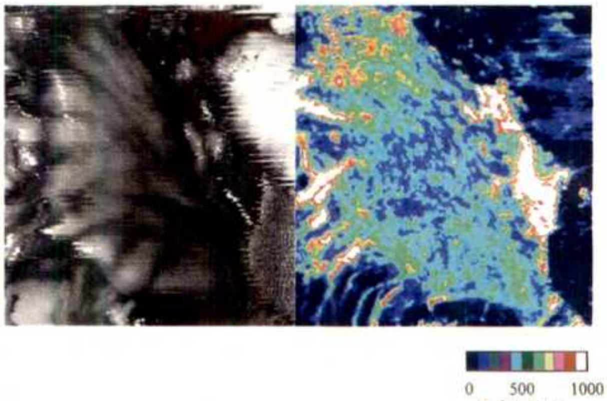

Fig. 1 Stomach before mobilization, with greater curve to the left and fundus at the bottom of the picture. The two images were made simultaneously by the laser Doppler scanner. In the colour perfusion map blood flow is colour coded and regions of interest can be outlined simultaneously on the black and white image. Note the uniform perfusion in all areas of the stomach. The liver is clearly demonstrated as are some vessels on the greater gastric curve coursing from the gastroepiploic arcade

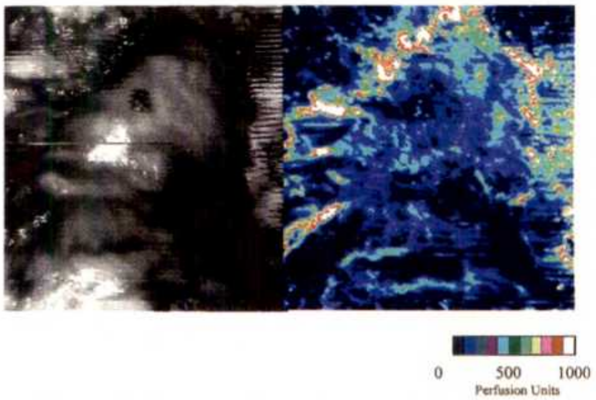

Fig. 2 Stomach following mobilization. Note the reduced flow in the fundus compared with the gastric antrum

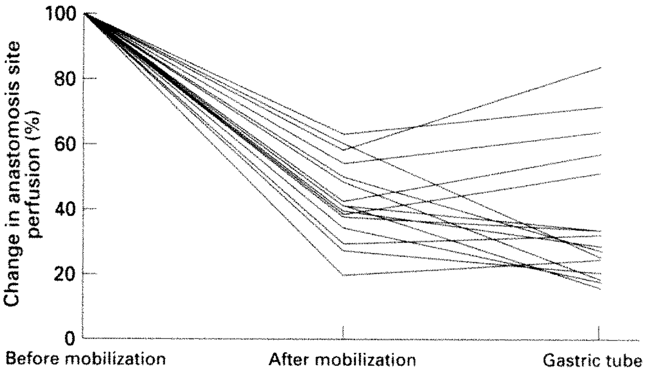

Fig. 3 Changes in anastomosis site perfusion following gastric mobilization and tube formation

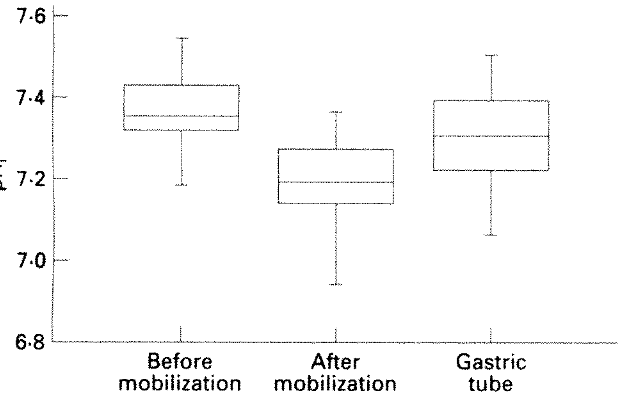

Fig. 4 Intraoperative gastric intramucosal pH (pH$_{\text{i}}$). Boxes show median (interquartile range) and bars the full range

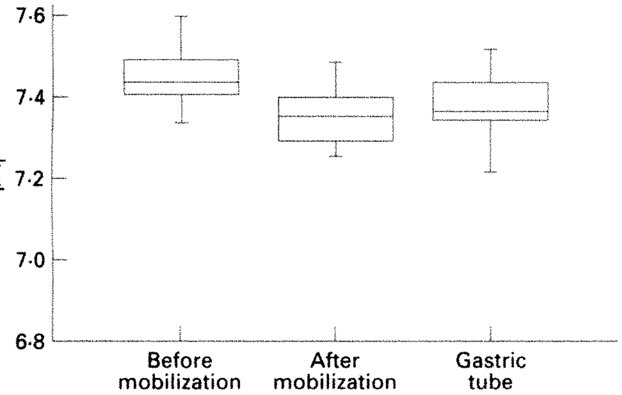

Fig. 5 Intraoperative jejunal intramucosal pH (pH$_{\text{i}}$). Boxes show median (interquartile range) and bars the full range

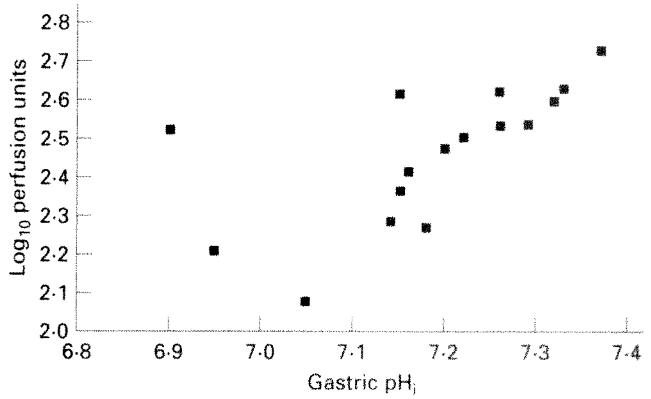

Fig. 6 Total gastric perfusion measured with the laser Doppler scanner and intramucosal pH (pH$_{\text{i}}$) following mobilization

at the anastomosis site where mean perfusion fell by 55 per cent from 519 to 234 PUs (*Fig. 3*). There was a gradient of reduced perfusion between this area and the antrum, where there was a reduction from 526 to 394 PUs (mean fall 25 per cent). These differences were clearly visible on the colour laser Doppler images but not to the surgeon's eye. After formation of the gastric tube and partial excision to the lesser curve there were further decreases in blood flow at the anastomosis site from 234 to 197 PUs (38 per cent of the original flow) and more proximally in the gastric body from 319 to 292 PUs (57 per cent of the original flow) but these falls did not reach statistical significance. In 12 patients fundal perfusion fell further following gastric tube formation but in seven there were increases following this manouevre.

In one patient who developed an anastomotic leak the gastric tonometer balloon failed between the post-mobilization and final measurements and it was therefore not possible to record a postanatomosis gastric pH$_{\text{i}}$. Before gastric mobilization mean gastric and jejunal pH$_{\text{i}}$ values were 7·37 and 7·46 respectively. These fell to 7·18 and 7·37 respectively following mobilization and, while mean gastric pH$_{\text{i}}$ rose to 7·29 after anastomosis, mean jejunal pH$_{\text{i}}$ rose by only 0·01 to 7·38 (*Table 2*; *Figs 4* and *5*).

In the five patients who developed an anastomotic leak or stricture there was a mean fall in perfusion at the anastomosis site, measured with the laser scanner, following gastric tube formation to 25 per cent of the premobilization value, which was lower than that in the remaining patients (mean fall to 33 per cent), but the difference was not statistically significant ($P = 0{\cdot}11$). There was no difference in pH$_{\text{i}}$ between the two groups of patients following anastomosis.

There was no significant relationship between laser Doppler measurements and gastric pH$_{\text{i}}$ before mobilization. However, subsequent to gastric mobilization there was a correlation between the two ($r = 0{\cdot}63$, $P = 0{\cdot}008$) (*Fig. 6*).

Table 2 Gastric and jejunal intramucosal pH during gastric mobilization and following anastomosis

	Before mobilization	After mobilization	*P**	After anastomosis	*P**
Gastric pH$_{\text{i}}$	7·37(0·09)	7·18(0·14)	0·0004	7·29(0·17)	0·55
Jejunal pH$_{\text{i}}$	7·46(0·07)	7·37(0·09)	0·0008	7·38(0·08)	0·30

Values are mean(s.d.). pH$_{\text{i}}$, intramucosal pH. *Wilcoxon signed rank test

Discussion

Following oesophagectomy and reconstitution of gastrointestinal continuity with a gastric tube, impaired anastomotic healing can lead to a postoperative leak in up to 26 per cent of patients and may account for up to 50 per cent of all perioperative deaths[17–19], while the formation of a benign stricture affects 7–40 per cent of patients[17,20]. Although several aetiological factors have been implicated in both of these complications, ischaemia at the site of anastomosis is thought to be important[21]. Following gastric mobilization and formation of a conventional pro-peristaltic gastric tube, the proximal stomach is vascularized only by an intramural plexus of vessels[22] and relies on the right gastroepiploic and sometimes right gastric arteries for its arterial inflow. The gastric fundus is the usual site of the oesophagogastric anastomosis and anatomical studies suggest that this part of the gastric tube has the most precarious tissue perfusion[23].

The intraoperative assessment of gastric perfusion particularly at the anastomosis site might enable a surgeon to predict anastomotic complications, and surgical or perhaps pharmacological manouevres might then prevent their occurrence. Laser Doppler flowmetry appears to be suited as a method of measuring tissue perfusion during operation. It is non-invasive, has been validated against other accepted techniques[2–9] in gastrointestinal tissues including the stomach, and has been employed previously at operation to assess changes in gastric[24,25], small bowel[26] and colonic[27] perfusion. There are several methodological drawbacks associated with the technique including the small sampling area and the necessity of contact between the probe and the tissue being sampled, which may itself influence local perfusion[28]. The sampling area of laser Doppler probes is dependent upon their geometry[29] but is usually between 1 and 3 cm^2, and because of blood flow heterogeneity within the wall of the gastrointestinal tract, single measurements may not be representative of overall perfusion. Previous studies employed multiple single-point measurements[24,25] but this is time consuming and not repeatable. SLDF appears to address the handicaps of single-point measurement. Since the laser beam is directed to the tissue and the reflected Doppler-shifted beam is received by a series of mirrors, there is no pressure applied to the tissue itself. The scans each took approximately 4 min, but this time could be reduced to less than 1 min by reducing the resolution. Each comprised up to 65 000 individual measurements of perfusion. The scanner's ability to sample from a wide area should circumvent the problems associated with blood flow heterogeneity.

The images produced by the scanner were easily interpreted and the differences in blood flow between the different regions of the stomach following both gastric mobilization and formation of the gastric tube, although not discernible to the surgeon's eye, were easily visible. The gradient of perfusion between the antrum and the fundus following division of the left and short gastric and left gastroepiploic arteries is consistent with previous results[25,30]. It is of note that in some patients perfusion at the anastomosis site fell considerably more than in others.

Conflicting evidence suggests that blood flow at depths of between 1 and 6 mm is measured[3,8,31] by lasers used in laser Doppler flowmetry and it is not known whether mucosal blood flow is detected by measurements taken from the serosal side of the human stomach. It has been demonstrated that mucosal pH_i is dependent upon mucosal blood flow and hypoxia[10,11], and that as splanchnic perfusion decreases there is increased local anaerobic energy production and a consequent linear decrease in pH_i[9]. The tonometric measurement of pH_i appears to predict postoperative complications thought to be caused by mucosal hypoperfusion. A low colonic pH_i has been found to predict anastomotic failure[32] and postoperative measurement of gastric pH_i appeared to predict subsequent anastomotic leak following oesophagectomy[14]. However, the traditional use of 0·9 per cent saline solution within the tonometer balloon as the vehicle for the carriage of carbon dioxide has been questioned recently[33]. Even with the use of correction factors, measurements taken involving equilibration periods of less than 30 min are likely to be inaccurate[34] and the method is therefore not suited to the measurement of pH_i at operation where the intraluminal environment is likely to be changing rapidly. RGT employs air as the vehicle for carbon dioxide. Equilibration from atmospheric P_{CO_2} to physiological levels is reached in 11 min[15] and, because the gas is automatically sampled and analysed, it is not subject to the errors involved in the manual sampling and analysis of saline.

In this study gastric pH_i fell following mobilization in all subjects, presumably consequent to partial devascularization. There were also falls in jejunal pH_i. As there was no significant change in systemic haemodynamics between the two measurements it is possible that this was caused by a splanchnic reflex directing blood away from the jejunum. Certainly differential regional changes in enteric pH_i have been demonstrated following incremental mesenteric occlusion in animals[10]. Following formation of the gastric tube and anastomosis, gastric pH_i rose. This may represent an improvement in mucosal perfusion within the remaining stomach following excision of the lesser curve. A mean fall from 313 to 256 PUs was recorded for the whole stomach between the end of gastric mobilization and gastric tube formation. It would therefore seem that the scanner is sampling blood flow within the serosa and muscularis but not the mucosa.

While there was no correlation between gastric pH_i and laser Doppler measurements before mobilization, following arterial division the changes were similar (*Fig. 6*). There is autoregulation of mucosal perfusion at high gastric flow rates but at lower flow rates mucosal perfusion enjoys a linear relationship with total arterial flow[35]. Findings in this study suggest that following mobilization the reduction in arterial flow may have been sufficient for both serosal–muscularis and mucosal perfusion to have become flow dependent and that the gastric mucosa had lost its autoregulatory ability.

Both of these new methods of assessing gastrointestinal perfusion are easily used at operation and appear to address the drawbacks of previous techniques. The images produced by the laser Doppler scanner permit serial measurement of changes in the distribution of blood flow within the stomach wall; these could be correlated with clinical outcome in future.

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Pain after groin hernia repair

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Background The purpose of the study was to provide a detailed description of postoperative pain after elective day-case open inguinal hernia repair under local anaesthesia.

Methods This was a prospective consecutive case series study. After 500 hernia operations in 466 unselected patients aged 18–90 years, pain was scored (none, light, moderate or severe) at rest, while coughing and during mobilization, daily for the first postoperative week and after 4 weeks. Pain scores were added together over the first postoperative week.

Results On days 1, 6 and 28, 66, 33 and 11 per cent respectively had moderate or severe pain while coughing or mobilizing. Total pain scores were higher while coughing or mobilizing than at rest ($P < 0\cdot001$). Younger patients had higher total pain scores than older patients while coughing or mobilizing ($P < 0\cdot01$), but not at rest. No significant differences were found between types of surgery or hernia.

Conclusion Pain remained a problem despite the pre-emptive use of opioids, non-steroidal anti-inflammatory drugs and local anaesthesia, irrespective of surgical technique.

Treatment of postoperative pain is important for humanitarian and ethical reasons, but may also have economic implications as pain may contribute to prolonged convalescence. Although pain and convalescence are important factors in the evaluation of surgical techniques for inguinal hernia repair (e.g. open *versus* laparoscopic operations), relatively little information is available from large-scale studies on the intensity and duration of pain after hernia repair[1].

This was a prospective study of pain after 500 consecutive hernia operations under standard anaesthesia and surgery to provide background information for further improvement of pain management.

Patients and methods

Data were collected prospectively from consecutive adult patients admitted for day-case elective repair of a reducible inguinal or femoral hernia under local anaesthesia between 1 September 1994 and 31 August 1996; 500 operations were studied. The study was approved by the local ethics committee and the Danish Data Protection Agency. Patients gave written informed consent to their participation.

Standard files providing detailed information about physical status, medication as well as hernia anatomy and type of repair were obtained. Questionnaires with prestamped return envelopes were given or mailed to the patient after surgery, seeking information about pain daily during the first postoperative week and after 4 weeks, use of analgesics and satisfaction with analgesic therapy. Pain was scored during rest, cough and mobilization (rise to sitting position) on a four-point verbal rank scale (none, light, moderate or severe).

Surgical and anaesthetic techniques

Several different repairs were employed depending on the type of hernia (*Table 1*)[2–4]. Unmonitored local anaesthesia and sedation were provided by the surgeon[5]. Bupivacaine 2·5 mg/ml was used for inguinal field block and local infiltration[6], and midazolam 1 mg/ml in small doses was used intravenously for sedation. For perioperative analgesia, oral tenoxicam, 40 mg in the evening and approximately 2 h before surgery, as well as 20 mg daily for 4 days after operation, was administered along with methadone orally 5–10 mg immediately before surgery and 5 mg 8 h after operation. Paracetamol 1–4 g per day was recommended as a supplementary analgesic.

Analysis

Descriptive statistics were used for demographics and pain course. Total pain scores (TPSs) during rest, cough or mobilization over the first week were obtained for each patient to avoid repeated comparisons at different time points. The

Table 1 Distribution of surgical techniques

Hernia type and surgical technique	*n*	Median age (years)
Primary direct inguinal; mesh repair	153	65
Primary indirect inguinal; herniotomy (sac excision)	22	35
Primary indirect inguinal; sac excision with internal ring repair	125	51
Primary indirect inguinal; modified mesh repair	57	69
Recurrent inguinal; mesh repair	91	63
Femoral; mesh repair, modified after McVay[3]	21	51
Other types of surgery (1 femoral, 11 recurrent inguinal)	12	57
Questionnaires not returned	19	61
Total	500	60

Interim results were presented to the International Symposium on Regional Anaesthesia, Auckland, New Zealand, 9–11 April 1996

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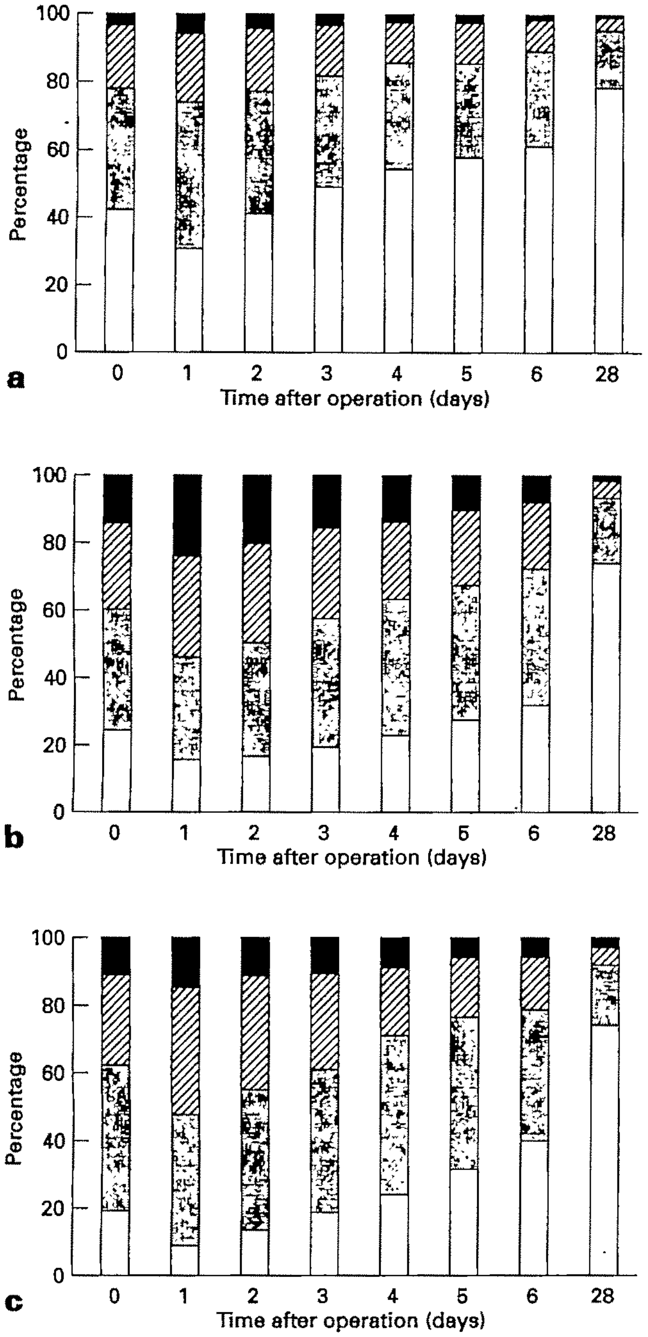

Fig. 1 Distribution of pain scores (percentage of patients) during the first postoperative week and after 4 weeks; a at rest, b while coughing and c during mobilization. Pain score: □, none; ░, light; ▨, moderate; ■, severe

Table 2 Percentage of patients having moderate or severe pain after inguinal hernia repair

	Day 1	Day 6	4 weeks
Rest	25 (21·1–28·8)	11 (8·2–13·8)	5 (3·0–7·0)
Cough or mobilization	66 (61·8–70·2)	33 (28·8–37·2)	11 (8·2–13·8)

Values in parentheses are 95 per cent confidence intervals

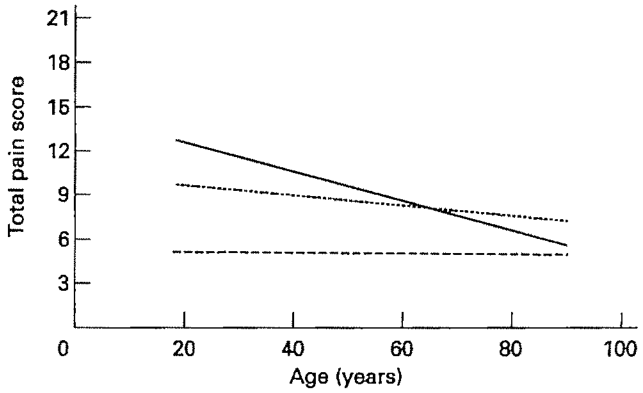

Fig. 2 Total pain score during the first postoperative week in relation to age shown as lines of linear regression ($n = 481$ hernia repairs; 19 of 500 questionnaires not returned). The negative correlation was statistically significant during mobilization (.......) ($P<0{\cdot}01$) and coughing (——) ($P<10^{-8}$), but not at rest (– – –) ($P>0{\cdot}3$) (Spearman correlation)

following values from the daily scores were used: 0, none; 1, light; 2, moderate; and 3, severe pain. Spearman rank order correlation coefficient, Friedman two-way analysis by ranks, Kruskal–Wallis test and Kolmogorov–Smirnov one-sample test were used as appropriate. $P<0{\cdot}05$ was considered statistically significant.

Results

Demographics

Five hundred operations were performed in 466 patients. Thirty-two patients had two operations, 13 due to recurrence of the hernia during the study interval, 19 with independent bilateral hernias, and one patient had three operations owing to two recurrences. There were 448 men and 52 women of median age 60 (range 18–90, interquartile range 44–74) years. According to the American Society of Anesthesiologists classification the patients belonged to groups I, II and III in 287, 175 and 38 instances respectively. Ninety-six per cent (481 of 500) of the 1-week questionnaires and 95 per cent (473 of 500) of the 4-week questionnaires were returned.

Overall pain scores

The distribution of pain scores over the first week is seen in *Fig. 1*. Maximum pain was reported on the first postoperative day, both with respect to pain at rest and during function (coughing or mobilization). The percentages (with 95 per cent confidence intervals) of patients having moderate or severe pain at rest or during function are shown in *Table 2*.

Forty-two per cent used paracetamol or another supplementary analgesic during the first postoperative week. Only 9 per cent were dissatisfied with the postoperative pain therapy.

For the entire cohort (as well as for all subgroupings) TPS was significantly lower at rest than during coughing or mobilization ($F_r = 298$, $P<0{\cdot}001$, Friedman test), with no difference between coughing and mobilization.

A statistically significant negative relation (Spearman rank order correlation) between age and TPS was seen during coughing ($r_S = -0{\cdot}303$, $P<10^{-8}$) and mobilization ($r_S = -0{\cdot}124$, $P<0{\cdot}01$), but not at rest ($r_S = -0{\cdot}023$,

$P > 0{\cdot}3$) (*Fig. 2*). The correlation between age and TPS was present in all subgroups of surgical technique during coughing and mobilization, although not always with statistical significance.

No subgroup of hernia type showed significant differences in TPS at rest, coughing or mobilization. There were no significant differences in TPS between Lichtenstein's mesh repair and other techniques used for repair of an indirect hernia. Patients with a femoral hernia treated with mesh repair modified after McVay[3] tended to have more pain during mobilization, with significantly higher pain scores than the cohort as a whole on days 4 and 6 ($P < 0{\cdot}05$).

Discussion

Little is known about pain after groin hernia repair from large-scale descriptive or even randomized studies[7]. The key results in the present study accord with those of previous smaller studies[8,9]. Moderate or severe pain during function was reported in 66 per cent of patients on day 1, in 33 per cent on day 6 and in 11 per cent after 4 weeks; the corresponding values at rest were 25, 11 and 5 per cent. Postoperative pain was not prevented despite extensive pre-emptive therapy by an inguinal field block and incisional local anaesthesia for the surgical procedure. This contrasts with the results of a comparison of spinal and general anaesthesia with and without preoperative incisional infiltration[10]. In addition, the results emphasize the importance of pain scoring under both rest and performance conditions. Young patients had more function-related pain, both in the entire cohort and for most of the different surgical techniques. A higher level of physical activity in younger patients, and perhaps more critical expectations for the postoperative course, are possible explanations for this finding. In other surgical settings a similar age dependency has been demonstrated[11,12]. The higher pain scores in young patients should be considered when analgesic therapy after hernia repair is studied or prescribed.

Neither the type of hernia nor the type of repair influenced postoperative pain scores in comparable groups. Nevertheless, until more data from controlled studies are available, it remains necessary, in future studies of pain after hernia repair, to standardize both description of hernia anatomy, type of surgery and anaesthetic technique.

As judged by the pain scores there is a need for analgesic therapy in a substantial number of patients even at the end of the first postoperative week. In this context, development of slow-release or long-acting local anaesthetic agents should receive increased attention[1].

It is surprising that 11 per cent had moderate or severe function-related pain after 4 weeks. Although the duration of convalescence is dependent on tradition and differing recommendations[13], pain of more than a few days' duration may certainly influence the return to work or normal activity. Although this may seem obvious, no studies have demonstrated the relation between pain and duration of convalescence. However, in 100 consecutive patients of the present cohort, pain was the primary reason for extension of a recommended convalescence time (data not shown)[14].

Pain remained a significant problem during the first postoperative week after open hernia repair, despite the use of pre-emptive local anaesthesia and multimodal postoperative analgesia. After 4 weeks a substantial number of patients still had function-related pain.

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Repair of ventral hernias with expanded polytetrafluoroethylene patch

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Background Operations for large and recurrent abdominal hernias have a high associated recurrence rate, although it is lower when prosthetic material is used. Expanded polytetrafluoroethylene (ePTFE) seems to be the best tolerated prosthetic material in surgery.

Methods A series of 45 ventral hernias repaired using ePTFE for closure or reinforcement of the herniorrhaphy has been evaluated prospectively. Thirty-six were midline incisional hernias and nine were transverse or pararectal ventral hernias. There were 13 recurrent ventral hernias and three defects were operated as an emergency procedure. The patch was sutured to the anterior aponeurosis with a running non-absorbable suture. Some other kind of intra-abdominal procedure was undertaken in 12 cases.

Results ePTFE was well tolerated. Complications occurred in five patients. Major complications were found in three patients: cutaneous necrosis requiring a myocutaneous flap; and infection of the prosthesis (primary, and secondary to enterocutaneous fistula due to diverticulitis, both requiring removal of the patch). Mean follow-up was 39 months and hernia recurrence occurred in only one patient.

Conclusion This clinical experience shows that ePTFE is a very reliable prosthetic material for the repair of abdominal wall hernias.

Surgery of large defects and recurrent hernias of the abdominal wall requires a safe and accurate technique. The best opportunity to repair an abdominal hernia definitively is at the first operation, and it should not be regarded as minor surgery. The treatment of these hernias is difficult using the usual techniques because of the large size of the defect or because of the low resistance of scarred tissues which have been weakened by age, infection or numerous operations. The basic principles for definitive correction involve the type of material used (non-absorbable monofilament is recommended) and tension-free reconstruction of the abdominal wall[1]. This is frequently achieved with prosthetic materials. Steel sutures and autologous grafts are no longer used[2,3]. Safe and comfortable synthetic materials have been developed in recent decades and should possess two properties: strength and good biological tolerance. Outstanding among these materials is expanded polytetrafluoroethylene (ePTFE), developed in 1976[4] (by expanding Teflon (Du Pont, Wilmington, Delaware, USA) into a porous material), which seems to fulfil both requirements; ePTFE appears to be superior to other materials such as Teflon, polypropylene and nylon[5]. In this study, clinical experience in the repair of incisional hernias and abdominal wall defects left after cancer surgery using an ePTFE prosthesis is analysed.

Patients and methods

Forty-five laparotomy incisional hernias (after exclusion of one patient lost to follow-up) were repaired using a 2-mm ePTFE patch (Gore-Tex Soft Tissue Patch; W. L. Gore, Arizona, USA) in 34 men and 11 women, aged between 20 and 74 (mean 55) years. The location and size of ventral hernias, as well as simultaneous intra-abdominal operations, are summarized in *Table 1*. The hernial defects were classified as small, medium or large, according to the greatest diameter of the implanted prosthesis: 10 cm or less, 11–19 cm or 20 cm or more respectively. Risk factors for recurrence are summarized in *Table 2*. One of the incisional hernias was secondary to excision of a melanoma, and two were abdominal wall defects repaired

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Table 1 Size of hernias and other abdominal procedures

	No.	Size of hernia (cm)*	Small	Medium	Large	Other procedures
Midline hernias	36	16 × 11	7	16	13	12
Supraumbilical	18	13 × 9 (6–25 × 5–20)	6	9	3	5
Infraumbilical	8	15 × 13 (7–25 × 5–7)	0	5	3	3
Supraumbilical and infraumbilical	10	21 × 13 (10–30 × 6–25)	1	2	7	4
Transverse incisional hernias	6	9 × 7	3	2	1	0
Subcostal laparotomy	2	12 × 10 (5–20 × 5–10)	1	0	1	0
Pfannenstiel laparotomy	2	12 × 8 (10–15 × 5–10)	0	2	0	0
McBurney incision	2	8 × 6 (7–9 × 4–6)	2	0	0	0
Pararectal hernia	3	7 × 6 (5–10 × 5–8)	1	2	0	0

*Values are mean (range)

Table 2 Risk factors for infection and hernia recurrence

	No.	Obesity	COPD	Immuno-depression†	Trans-plant	Infec-tion‡	Peritoneal opening	Previous operations*	Previous herniorrhaphies*
Midline hernias	36	14	4	12	2	5	18	1·8	0·3
Supraumbilical	18	9	3	4	2	3	8	1·7 (1–3)	0·4 (0–2)
Infraumbilical	8	2		4			3	2·4 (1–4)	0·4 (0–1)
Supraumbilical and infraumbilical	10	3	1	4		2	7	1·5 (1–3)	0·1 (0–1)
Transverse incisional hernias	6	2		3				1·8	0·15
Subcostal laparotomy	2	1		1				2·5 (1–4)	0·5 (0–1)
Pfannenstiel laparotomy	2			2				2 (2–2)	0·5 (0–1)
McBurney incision	2	1						1 (1–1)	0
Pararectal hernias	3	1			1	1	2	2·7 (1–4)	1 (0–2)

*Values are mean (range). †General immunodepression (cancer, chemotherapy, splenectomy, diabetes). ‡Operated as emergency surgery (evisceration, intestinal obstruction, etc.) or in an infected or open wound. COPD, chronic obstructive pulmonary disease

primarily after oncological resection of tumours. Three patients underwent repair as an emergency procedure: dehiscence of a pararectal laparotomy wound for a kidney transplant, intestinal obstruction due to incarceration and infection of a Prolene (Ethicon, Edinburgh, UK) mesh. In some instances other surgical abdominal procedures accompanied the repair: cholecystectomy (three patients), small bowel resection (two), anterior resection of the rectum for cancer, colostomy, second look for ovarian cancer, colostomy reversal, abdominal wall tumour resection, adhesiolysis and parastomal herniorrhaphy. Seven patients had previously undergone repair with prosthetic material and were referred after hernia recurrence: ePTFE patch (four patients whose prosthesis had been sutured with interrupted stitches, either as an onlay or subfascial herniorrhaphy), Prolene mesh (two) and Lyodura (B/Braun, Melsungen, Germany) patch (one). Thirteen of the 45 hernias had already been repaired at least once (*Table 2*).

The operations were carried out under general anaesthesia, and the patients were given antibiotic prophylaxis before and after operation. After discharge, all patients were followed up after 1 month, 3 months, yearly and in October 1997, so that any complications or recurrence could be assessed.

Surgical technique

The cutaneous flaps were dissected widely until the healthy aponeurosis and scar edges of the hernial ring could be identified and protected with laparotomy pads soaked in povidone–iodine solution. The peritoneal sac was opened in 21 patients: in 12 for some other intra-abdominal procedure, in one patient with incarcerated hernia, in one with evisceration and in some patients in whom the ring was narrow or the peritoneal sac was redundant. After cleaning the fibrous edges of the hernial ring in smaller hernias, the edges were sutured in the midline whenever possible for a reasonably tension-free closure with one-layer sutures of a non-absorbable monofilament material (polypropylene 1), or a . long-term absorbable suture (polygluconate 0, Maxon; Davis and Geck, Gosport, UK). At a later stage, 2-mm Gore-Tex prostheses were sutured tension-free with large bites to the healthy anterior aponeurosis of the rectus 2 cm from the hernial ring with at least eight single cardinal stitches of polygluconate (or every 5 cm if cardinal stitches were further apart in large hernias) and a running suture every 5 mm of Gore-Tex CV3, 3 mm from the prosthesis edge.

Two different techniques for repair were used. (1) With medium-sized oval patches of Gore-Tex to cover any possible recurrence, when the abdominal wall had been closed without undue tension, but appeared to be intrinsically weak (onlay reinforcement repair). This technique was used in 11 patients. (2) With large patches of Gore-Tex sutured to the edges of the hernial ring, when the size of the ventral hernia did not allow closure in the midline. This technique was used in 34 patients.

After haemostasis and cleansing of the wound, one or two suction drains were left under the subcutaneous layer. The subcutaneous tissue was closed using absorbable material, and the skin with clips. The drains were left in position until daily output fell below 30 ml.

Results

There were no operative deaths. At present, after a median follow-up of 39 (6–92) months, one patient has died from cardiac failure 8 months after surgery. There were five patients with early complications: (1) cutaneous necrosis caused by lack of subcutaneous tissue between the skin and the peritoneum in a large ventral hernia which had been developing over 40 years; a vascularized free flap of latissimus dorsi and skin grafts were required, but the prosthesis was not withdrawn and the patient did not experience further complications; (2) enterocutaneous fistula as a result of postoperative perforated diverticulitis, with removal of the Gore-Tex patch, resection of the colon and primary closure of the laparotomy (after 6 years the hernia had not recurred); (3) one primary infection of the surgical wound that initially required drainage and more recently required withdrawal of the prosthesis and primary closure of the abdominal wall with extensive relaxing incisions to the anterior fascia; and (4) two cases of seroma requiring aspiration. There were no haematomas. The only late complication was a wound sinus; on removal of an offending stitch the area healed. *Table 3* summarizes the results of six abdominal reoperations in

Table 3 Reoperations after hernia repair

Time after herniorrhaphy (years)	Surgical procedure	Complications
1	Full-thickness cutaneous resection	No
1*	Right hemicolectomy (malignant intestinal obstruction)	No
2*	Left hepatectomy (liver metastasis)	No
2	Total colectomy and ileostomy	No
4	Adhesiolysis	Wound infection, healing after drainage
4	Resection of rectal cancer recurrence	No

*The same 75-year-old patient

which the wound of the prosthesis was opened, and the results as far as wound infection is concerned. No hernia recurrence has been diagnosed in these five patients. At follow-up in October 1997, one of 43 evaluable patients had developed hernia recurrence, consisting of a recurrence 2 cm in diameter just above a reinforcement patch, probably not detected at the hernia repair; this was reoperated on 4 years after the operation and had not recurred after 7 years. The results in terms of aesthetics and patient comfort have proved satisfactory for the whole series.

Discussion

Recurrent and incisional hernias occur frequently after abdominal surgery[6]. In many series of ventral hernia repairs a high percentage of patients have been operated on several times[1], which may account for the lack of resilience in the musculoaponeurotic abdominal wall layer and the size of the hernias, the edges of which could only be held together under unacceptable tension for healing[3]. To avoid such tension and further weakening of the tissues and recurrences, prosthetic materials have been used since the end of the last century[7]. Synthetic plastics have been used only since the 1950s[7–9]. Among these, only Dacron (Du Pont) and polypropylene, the newest high-density version of polyethylene (Marlex (C. R. Bard, Billerica, Massachusetts, USA) or Prolene) have proved to be effective in preventing recurrence[7,9]. Marlex is commonly used in the repair of incisional and other ventral hernias[10], and possesses most of the properties required for a prosthetic material (strength, durability, tolerance, porosity)[7]. However, even though the short-term results are good[9,10], it has two major drawbacks: it induces adhesions and considerable fibrosis which in the long term may cause bowel adhesions, cutaneous ulceration, gastrointestinal fistula, recurrence and displacement of the prosthesis[11–14].

Gore-Tex adds porosity as an important characteristic in prosthetic materials[7,15] which facilitates its incorporation into the tissues and the penetration of connective tissue[7,15]. A few years' use of ePTFE in vascular prostheses proved that this material has good tolerance and a very low propensity to infection[16,17], and it was then used in the repair of abdominal hernias[15,18,19], where it was well tolerated, even after infection, with an incidence of hernial recurrence around 10 per cent in preliminary clinical reports[15]. These results are similar to those obtained using Marlex[9,10,20]. However, in the present study the incidence of hernial recurrence after repair of ventral hernias with ePTFE was 2·3 per cent (one of 43). It is preferable not to open the peritoneal sac. The prosthesis should be anchored to the anterior aponeurosis using a running Gore-Tex CV3 suture and some interrupted stitches of monofilament or Gore-Tex material. Mattress stitches to suture the patch were not used.

As far as tolerance of the prosthetic material, and low rate of infections and hernia recurrence are concerned, the results achieved in this clinical study indicate that ePTFE is one of the best prosthetic materials at present available for the repair of ventral hernias. It is soft, pliable and comfortable, does not produce scar rigidity, and is extremely well tolerated. Other clinical and experimental studies using ePTFE do not report severe complications[15,18,19,21,22], such as those sometimes found with Marlex, and the histological evidence shows that it integrates well within tissues[15]. The technique for implanting and suturing the patch in the repair of ventral hernias, without tension and mattress sutures, has shown itself to be effective here, as in Bauer's series[15]. In contrast with the results obtained by other authors using separate stitches (which were perhaps spaced too widely)[15,18,19], the running Gore-Tex suture, with aponeurotic stitches close together, may enable the onlay patch to adapt well to the healthy aponeurosis, offers a more secure form of fixation and prevents small button-hole hernia recurrences between single stitches which are too far apart or become untied. Nevertheless, long-term follow-up data after this particular technique are not yet available. However, the use of mattress sutures to fix the ePTFE patch in a preperitoneal position is complicated in comparison to use of a tension-free Gore-Tex suture in an onlay position, although excellent preliminary results with the U sutures technique (Rives technique) through the full thickness of the abdominal wall have been reported with ePTFE (0–5 per cent recurrence rate)[18,23,24].

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Experimental study of the effect of intra-abdominal pressure during laparoscopy on tumour growth and port site metastasis

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Background The influence of raised intraperitoneal pressure during laparoscopy on tumour growth and port site metastasis is still unknown.

Methods Tumour growth of colonic adenocarcinoma DHD/K12/TRb was measured after laparoscopy with carbon dioxide at different pressures (0, 5, 10 and 15 mmHg) in a rat model. Cell kinetics were determined after incubation with carbon dioxide (0, 5, 10 and 15 mmHg) *in vitro* ($n = 60$). Additionally, tumour growth was measured subcutaneously and intraperitoneally 4 weeks after laparoscopy at different intraperitoneal pressures (5, 10 and 15 mmHg) ($n = 100$).

Results *In vitro* tumour growth decreased significantly after incubation with carbon dioxide at 10 and 15 mmHg compared with a pressure of 0 or 5 mmHg. *In vivo*, mean(s.d.) intraperitoneal tumour weight was significantly increased after laparoscopy at 5 mmHg (919(1085) mg) and at 10 mmHg (1274(1523) mg) ($P < 0{\cdot}05$), but decreased again after laparoscopy with an intraperitoneal pressure of 15 mmHg (731(929) mg) compared with the control group (365(353) mg) ($P = 0{\cdot}3$). Mean(s.d.) subcutaneous tumour growth was promoted after laparoscopy at 5 mmHg (172(234) mg), at 10 mmHg (190(253) mg) and at 15 mmHg (178(194) mg) compared with controls (48(33) mg) ($P < 0{\cdot}05$).

Conclusion *In vitro*, raised intraperitoneal pressure leads to suppression of tumour growth. *In vivo*, intraperitoneal tumour growth is suppressed only by higher pressure (15 mmHg). Subcutaneous tumour growth is stimulated by carbon dioxide independently of the intraperitoneal pressure.

Port site metastasis and early tumour recurrence after laparoscopic procedures in the presence of intra-abdominal malignancy have led to controversy over the use of these techniques in patients with cancer[1–7]. It seems that tumour seeding and development of subcutaneous metastases appear more often after laparoscopic than after open resection of malignant tumours. The mechanism for this phenomenon remains unclear[8–10], although it has been demonstrated that incubation of tumour cells with carbon dioxide leads to increased tumour growth *in vitro* and *in vivo*, whereas incubation with helium does not stimulate tumour growth[11]. Many other factors certainly also influence tumour growth *in vivo* and utilization of carbon dioxide may be only one of many factors implicated in the promotion of tumour growth.

One factor, which has not yet been evaluated, may be the influence of raised intraperitoneal pressure during the establishment of a pneumoperitoneum. Increased intraperitoneal pressure itself may have a direct influence on tumour cells or may even lead to postoperative immunological changes in the tumour host resulting in promotion of tumour growth after laparoscopic surgery. Therefore, the influence of different intraperitoneal pressures during gas incubation with carbon dioxide on tumour growth was investigated *in vitro* and in a rat model.

Materials and methods

In the first experiment the influence of carbon dioxide at different pressures was investigated *in vitro* to distinguish between direct influences of the different pressures during gas incubation and the reactions of the tumour host. The hypothesis underlying this experiment was that there is no difference in tumour growth between the different pressures during incubation with carbon dioxide *in vitro*.

Colonic carcinoma cell line DHD/K12/TRb cells (ECACC) were cultured in Dulbecco's MEM (Biochrom, Berlin, Germany) and Hams F10 medium (Biochrom) supplemented 1:1 (volume) with 10 per cent fetal bovine serum (Gibco, Eggenstein, Germany), glutamine 2 mmol/l (Biochrom) and penicillin–streptomycin (Gibco) 100 units/ml. Cells were cultured for at least 7 days and the numbers of viable cells were determined by staining with acridine orange and fluorescence microscopy in a Neubauer counting chamber before the *in vitro* experiments.

Some 5×10^6 cells were suspended in 10 ml culture medium. The cells were incubated with pure carbon dioxide under different pressures (0, 5, 10 and 15 mmHg). The gas was insufflated into culture flasks (75 cm^2 per 250 ml) through a sterile filter and drawn out through a control valve. The mean pressure during incubation was $0 \pm 0{\cdot}5$ mmHg in the first group, $5 \pm 0{\cdot}5$ mmHg in the second group, 10 ± 1 mmHg in the third group and 15 ± 1 mmHg in the fourth group. After 3 h of incubation, the cells were washed twice, resuspended and cultured in 12 wells (1·88 cm^2) at a concentration of 10^4 viable tumour cells per well. Three wells of each group were washed twice with phosphate-buffered saline (Charité, Berlin, Germany) after 24 h and incubated with 300 μl 0·05 per cent trypsin in 0·02 per cent ethylenediamine tetra-acetic acid (Biochrom) for 30 min at 37°C to remove adherent cells. Viable and dead cells were counted after staining with acridine orange by fluorescence microscopy every 24 h over 5 days. Experiments were repeated five times so that 15 wells in each group were evaluated every 24 h.

In the second experiment, the influence of different intraperitoneal pressures (5, 10 and 15 mmHg) during laparoscopy with carbon dioxide was investigated after intraperitoneal and subcutaneous inoculation of tumour cells. Tumour growth was measured 4 weeks after application. The animal model used in this study is well established and it is

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known that rat colonic carcinoma DHD/K12/TRb grows in small nodules when injected subcutaneously or intraperitoneally in syngeneic animals[11]. The hypothesis of this experiment was that there is a positive correlation between raised intraperitoneal pressure and increased tumour growth. Intraperitoneal and subcutaneous injection was performed to evaluate the effects of increased intraperitoneal pressure on different tumour sites.

One hundred male inbred BD IX · rats 2 months old (Iffa-Credo, L'Arbresle, France) were acclimatized in a climate- and light cycle-controlled environment for at least 7 days before investigation. The animals were allowed standard laboratory food and water *ad libitum*. All studies were performed under protocols approved by the local committees of animal use and care.

Some 1×10^4 cancer cells in 1 ml culture medium were applied intraperitoneally and subcutaneously by sterile injection in all animals. The rats were randomized into four different groups. Three trocars (Miniport ϕ 2 mm; AutoSuture, Norwalk, Connecticut, USA) were installed through the abdominal wall in all groups to evaluate the development of tumour growth at these sites. In the first group ($n = 25$) laparoscopy was performed with insufflation of pure carbon dioxide at a pressure of 5 mmHg over 30 min. In the second group ($n = 25$) laparoscopy was performed at 10 mmHg, and 15 mmHg was used in the third group ($n = 25$). The control group ($n = 25$) underwent no further manipulation after cell injection, and placement of the trocars and anaesthesia was continued for 30 min. The animals were killed 4 weeks after interventions, tumour nodes were excised intraperitoneally and subcutaneously, and the weights were assessed on a balance. Additionally, numbers and distribution of intraperitoneal tumour nodes were investigated in all animals. It has been shown in previous studies that excision of the tumour nodes is a precise and reproducible method because the tumour is growing in small nodules rather than infiltrating the surrounding tissue[11].

Statistical analysis

Data are given as mean(s.d.). Results between groups were compared with the Kruskal–Wallis or Mann–Whitney *U* test for continuous data and Fisher's exact test for categorical data, if appropriate. $P < 0{\cdot}05$ was considered significant.

Results

Tumour growth in vitro

Tumour cells were grown over 5 days in all groups (*Fig. 1*). Insufflation with carbon dioxide at 10 and 15 mmHg caused a significant decrease in tumour cell growth *in vitro* compared with that in the other groups (0 and 5 mmHg) ($P < 0{\cdot}05$) from day 2 to day 5. Tumour growth showed a significant difference between 0 mmHg and 5 mmHg only at day 2 ($P < 0{\cdot}05$). Tumour cell growth was most suppressed at gas incubation with a pressure of 15 mmHg.

Tumour growth in vivo

In vivo, intraperitoneal tumour weights differed ($P = 0{\cdot}007$) between the four groups (*Fig. 2*). Mean(s.d.) weights were significantly higher in the laparoscopy group with carbon dioxide at 5 mmHg (919(1085) mg) and at 10 mmHg (1274(1523) mg) ($P < 0{\cdot}05$), but decreased again after laparoscopy with an intraperitoneal pressure of 15 mmHg (731(929) mg) compared with the control group (365(353) mg) ($P = 0{\cdot}3$). The number of intraperitoneal metastases was significantly higher than for controls only in rats that received laparoscopy with an intraperitoneal pressure of 5 mmHg ($P < 0{\cdot}05$). Numbers were also markedly increased at 10 mmHg but were not significantly different because of high standard deviations. There was

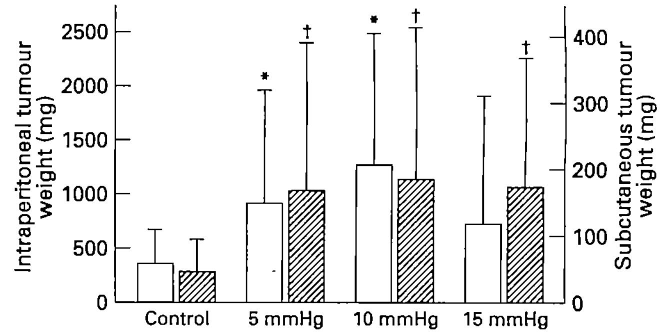

Fig. 2 Weight of intraperitoneal (□) and subcutaneous (▨) tumours 4 weeks after cell instillation and insufflation ($n = 25$ rats in each group). Values are mean(s.d.). $^*P < 0{\cdot}05$ (intraperitoneal tumour weight at 5 and 10 mmHg *versus* control group); $^†P < 0{\cdot}05$ (subcutaneous tumour weight at 5, 10 and 15 mmHg *versus* control group) (Kruskal–Wallis test)

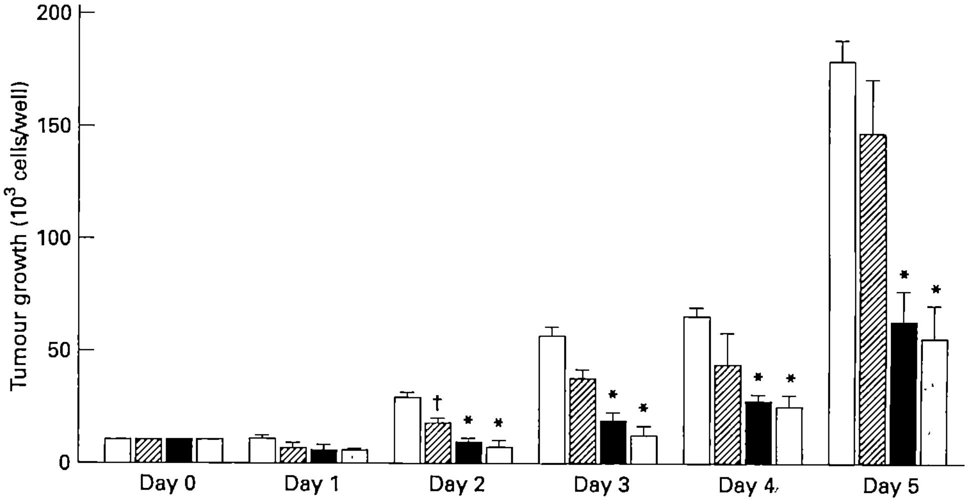

Fig. 1 *In vitro* tumour cell growth after insufflation with carbon dioxide at different pressures (□, 0 mmHg; ▨, 5 mmHg; ■, 10 mmHg; ⊡, 15 mmHg; $n = 15$ in each group). Values are mean(s.d.). $^*P < 0{\cdot}05$ (0 and 5 mmHg *versus* 10 and 15 mmHg) (Kruskal–Wallis test); $^†P < 0{\cdot}05$ (0 mmHg *versus* 5 mmHg) (Mann–Whitney *U* test)

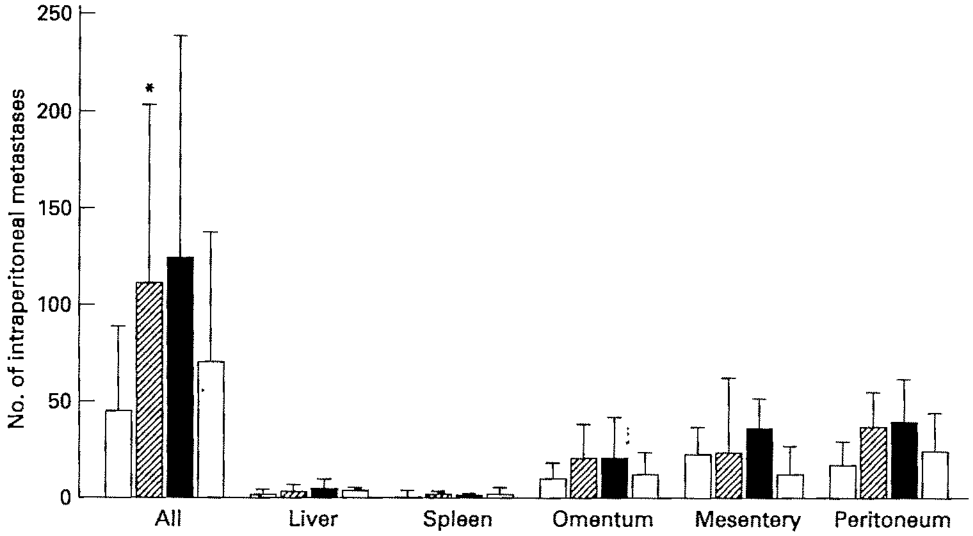

Fig. 3 Number and distribution of intraperitoneal metastases 4 weeks after cell instillation and insufflation (□, 0 mmHg; ▨, 5 mmHg; ■, 10 mmHg; □, 15 mmHg; $n = 25$ animals in each group). Values are mean(s.d.). $^*P<0{\cdot}05$ (laparoscopy at a pressure of 5 mmHg *versus* control group, Mann–Whitney U test)

no difference in the distribution of tumour nodules among the four groups (*Fig. 3*).

In comparison to intraperitoneal tumour, subcutaneous tumour growth was promoted after laparoscopy at 5 mmHg (172(234) mg), at 10 mmHg (190(253) mg) and at 15 mmHg (178(194) mg) compared with the control group (48(33) mg) ($P<0{\cdot}05$) (*Fig. 2*). The total number of tumour metastases was also increased at port sites in all groups with raised intraperitoneal pressure (5 mmHg, $n=48$; 10 mmHg, $n=42$; and 15 mmHg, $n=45$) compared with controls ($P<0{\cdot}05$) ($n=22$).

Discussion

Enthusiasm for the use of laparoscopic techniques in patients with malignant disease has been diminished by reports of early port site recurrence after laparoscopic procedures[1–7]. Carbon dioxide is commonly used to establish the pneumoperitoneum and it may have an influence on tumour growth. In different experimental studies insufflation of carbon dioxide has been found to cause promotion of tumour growth *in vitro*, *ex vivo* and *in vivo*[11]. The frequency of tumour growth at trocar sites was increased after laparoscopy with carbon dioxide, indicating that carbon dioxide is an important factor in the aetiology of early port site recurrence[11,12].

Besides carbon dioxide, other factors may also influence tumour growth during laparoscopy. Increased intraperitoneal pressure is also present and may influence tumour growth at trocar incision sites and in the abdominal cavity. Experimental studies of tumour growth at different raised intraperitoneal pressures have not yet been evaluated.

In the first experiment, the direct influence of different pressures on tumour cells during incubation with carbon dioxide was investigated *in vitro*. Cell growth of the adenocarcinoma cell line was suppressed significantly after insufflation with carbon dioxide at pressures of 10 and 15 mmHg compared with the control group (0 mmHg), while lower pressure (5 mmHg) caused only minor changes in tumour cell growth. It is hypothesized that increased pressure leads to suppression of tumour cell growth as a result of direct damage to the cell membrane of the tumour cells, leading to increased cell death *in vitro*. Further *in vitro* investigations are needed to elucidate the pathophysiological mechanisms of these observations.

In the second experiment, the effect of pneumoperitoneum with carbon dioxide at a pressure of 5, 10 and 15 mmHg was investigated *in vivo*. Intraperitoneal tumour growth was significantly increased after insufflation of carbon dioxide at lower intraperitoneal pressures (5 and 10 mmHg) compared with the control group. Interestingly, intraperitoneal pressure of 15 mmHg during laparoscopy led to a reduction of intraperitoneal tumour growth and showed no difference to the control group. These results can be explained by different mechanisms. In other experiments carbon dioxide has been shown to stimulate tumour growth *in vitro* and *in vivo* at an intraperitoneal pressure of 8 mmHg[11]. This stimulation could be responsible for increased tumour growth at lower pressures. Furthermore, increased intraperitoneal pressure may also cause immunsuppression in the tumour host leading to increased tumour growth. On the other hand, higher pressures may produce damage to the tumour cells in the peritoneal cavity itself, as shown in the *in vitro* experiments. This phenomenon could theoretically explain the decreased tumour growth in the group subjected to 15 mmHg although carbon dioxide is stimulating the cells at the same time.

In contrast, subcutaneous tumour growth was significantly stimulated in all groups with raised intraperitoneal pressures when compared with the control group. One reason for the stimulation of subcutaneous tumour growth may be the insufflation of carbon dioxide, as shown in previous studies[11]. Thus, it seems that carbon dioxide acts not only locally in the intraperitoneal cavity but also systemically at other sites. The high solubility of carbon dioxide may explain the promotion of tumour growth in subcutaneous tissue and at abdominal incisions in the rat model. Additionally, direct damage to the cells by increased pressure may not occur in subcutaneous tissue and therefore tumour growth is increased in all groups at this site. Furthermore, increased intraperitoneal pressure may also lead to perioperative immune suppression due to an increase of tumour growth. Vallina and Velasco[13] found a significant decrease in the T helper to T suppressor cell ratio after laparoscopic cholecystectomy, although it has been demonstrated in different studies[8-10] that laparoscopy leads to better postoperative preservation of immune response than laparotomy.

To avoid the negative effects of raised intraperitoneal pressure and carbon dioxide on subcutaneous tumour growth and port site metastases, gasless laparoscopy might be preferable in the treatment of patients with cancer. Bouvy *et al.*[12] demonstrated that tumour growth shows no significant stimulation after gasless laparoscopy compared with laparoscopy with carbon dioxide and raised intra-abdominal pressure in a rat model.

In conclusion, the results of this study indicate that raised pressure during gas incubation leads to suppression of tumour growth *in vitro*, possibly as a result of direct damage to the cells. Nevertheless, laparoscopy with carbon dioxide and slightly increased intraperitoneal pressure (5 and 10 mmHg) leads to promotion of intraperitoneal tumour growth *in vivo*. Higher pressure (15 mmHg) again causes suppression of intraperitoneal tumour growth. In contrast, subcutaneous tumour growth is stimulated by carbon dioxide insufflation and different raised intraperitoneal pressures. The hypothesis that increased intraperitoneal pressure might influence the immune system of the tumour host and increase immune suppression after laparoscopy remains theoretical and requires further study.

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Results of surgical resection of liver metastases from non-colorectal primaries

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Background Advances in the field of liver surgery have lowered its associated mortality and morbidity rates, and hepatic resection for metastatic disease is increasingly performed. There are few well defined guidelines for the heterogeneous group of non-colorectal metastases. This study analysed the risks and benefits of surgical resection for liver metastases from non-colorectal primaries.

Methods A retrospective study was performed of 34 patients who underwent 37 operations over a 10-year period. Compilation of data from 141 patients from eight additional recent series was performed in order to analyse the effect of histological type on survival.

Results There were no perioperative deaths. Complications occurred after seven of 37 procedures. Actuarial survival rates were 61, 43 and 27 per cent at 1, 2 and 5 years. Survival was significantly improved for curative *versus* palliative resection ($P < 0{\cdot}05$), and for single *versus* multiple metastases ($P < 0{\cdot}05$). A strong correlation was observed between time to presentation with metastasis and length of survival ($P < 0{\cdot}0001$). Survival was significantly better for patients with secondaries from neuroendocrine tumours ($P < 0{\cdot}0001$), worse for those with intestinal adenocarcinomas ($P < 0{\cdot}0001$) and similar for patients with breast carcinoma ($P > 0{\cdot}5$) when compared with the whole group.

Conclusion The low mortality and morbidity rates and the satisfactory survival figures reported justify this type of surgery for selected patients, in the absence of therapeutic alternatives.

Surgery remains central to the curative approach to a majority of solid tumours, whether or not it is associated with chemotherapy or radiotherapy. When disease has become metastatic, the performance of an operation may seem to be a disproportionate act and is generally palliative. However, experience has shown that, occasionally, resection of metastases results in surprisingly long survival and even cure. These cases remain uncommon, but above all unpredictable[1–4]. Resection of hepatic metastases has been performed more frequently in the past 20 years, because of advances in anaesthetic management and surgical techniques and technologies, as well as a better understanding of the functional anatomy of the liver[4–8]. It has been clearly established that resection of liver metastases is feasible, but it remains to be proven that it is appropriate. Series of resection of liver metastases from colorectal primaries with precise guidelines abound in the medical literature[2], but reports and guidelines regarding surgery for metastases of other origins are lacking. Moreover, in most available series, the patients form a heterogeneous group, and therefore the results must be analysed with caution[9–16]. To establish the validity of this type of surgery, risks have to be balanced with benefits, and survival rates achieved must be compared with those obtained by non-surgical cancer therapies. Comparison could also be made with the results of resection of metastases from colorectal primaries.

The purpose of this study was to review the experience of a single unit with liver resection for non-colorectal metastases, and to compare it with available data from other sources, in order to determine whether this type of surgery can be vindicated in terms of risks and benefits, and which subsets of patients could be selected for it.

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Patients and methods

From January 1986 to December 1995 (10 years) 301 hepatectomies were performed. The records of 34 of these patients, who underwent 37 hepatectomies for liver metastases from non-colorectal primaries, were reviewed. This group consisted of 16 women and 18 men, with ages at the time of first operation ranging from 23 to 81 (median 54) years. *Table 1* shows the origin of the metastases. Discovery of the metastases and the primary tumour was synchronous in 12 patients and metachronous in 22. The median disease-free interval was 36 (range 10–160) months for the metachronous group. Eighteen patients had single metastases and 16 had multiple metastases; metastases with smaller satellite nodules were considered as single metastases.

Table 1 Origin of 34 non-colorectal primary tumours

	No. of patients
Carcinomas	
Neuroendocrine tumours	8
Breast	3
Lung	3
Pancreas	2
Uterus	2
Stomach	2
Ovary	1
Ampulla of Vater	1
Adrenal glands	1
Anus	1
Kidney	1
Adenocarcinoma of unknown origin	1
Total	26
Sarcomas	
Melanoma	4
Other	4
Total	8

Couinaud's description of the functional anatomy of the liver was used for designation of the segments and definitions of hepatectomies[17]. Resections were considered as major if three segments or more were removed according to Couinaud's classification.

Perioperative mortality and morbidity rates were calculated for the first 30 days after surgery or until discharge from hospital. Only patients with complications of grade II or over, according to Clavien *et al.*[18], were considered for analysis of morbidity. In brief, this applies to complications that threatened life, required surgical or drainage procedures, caused residual disability or prolonged hospitalization to twice the median postoperative hospital stay. Follow-up was available for all patients but one, who was lost to follow-up after 49 months with no evidence of recurrence at that time. Duration of follow-up ranged from 10 months to 10 years (median 31 months) for survivors.

A comprehensive review of all series of hepatectomy for non-colorectal secondaries published in the past 10 years (1986–1996) was also undertaken. Series with survival and histological data available for each individual patient were selected[13–16,19–22], and the figures were combined for determination of actuarial survival. Case reports were not considered. Survival was calculated from the time of the first operation.

Actuarial survival curves were obtained according to the Kaplan–Meier method. Statistical analysis was carried out with the Mantel–Cox log rank test for comparison of survival curves. Unpaired Student's t test was used for comparison of continuous variables. P values of less than 0·05 were considered significant.

Results

Twenty-one major hepatectomies and 16 minor resections were performed in this series (*Table 2*). All patients had had previous resection of the primary tumour, or had resection of the primary simultaneously with hepatectomy in the presence of synchronous metastases, except for one patient in whom the primary tumour was an adenocarcinoma of unknown origin. Surgery was performed with curative intent in 26 cases and for palliation in 11. After abdominal exploration and histological examination of the margins, resection was considered curative in 19 cases and palliative in 18. One patient underwent simultaneous resection of a lung metastasis, five had simultaneous resection of extrahepatic intra-abdominal metastatic nodules and four additional patients had simultaneous resection or ethanolization of tumour located in the other hepatic lobe. All of these ten patients were considered to have had palliative surgery. There were no perioperative deaths. Seven operations were followed by significant complications, which are shown in *Table 3*. Postoperative hospital stay ranged from 6 to 32 (median 15) days.

Table 2 Type of hepatectomy for 37 resections of liver metastases

Hepatectomy	No. of procedures
Major hepatectomy	21
Extended right hepatectomy	9
Right hepatectomy	9
Extended left hepatectomy	2
Left hepatectomy	1
Minor hepatectomy	16
Left lobectomy	5
Bisegmentectomy	1
Segmentectomy	1
Metastasectomy	9

Table 3 Complications following seven of 37 resections of liver metastases

Complication	No.
Biliary leak	2
Jaundice	1
Ileoileal intussusception	1
Adrenocortical insufficiency	1
Pleural effusion	4
Atelectasis	3
Lung infection	2
Pulmonary embolism	1
Pericardial effusion	1

Several patients suffered more than one complication

Complementary treatment after resectional surgery was given to 14 patients: nine patients received chemotherapy, four had iterative sessions of chemotherapy and chemoembolization of recurrences or contralateral lesions, and one patient had ethanolization of recurrences.

The overall actuarial survival rate was 61 per cent at 1 year, 43 per cent at 2 years, 39 per cent at 3 years and 27 per cent at 5 years. Median survival was 19 months (95 per cent confidence interval 11 months to 4 years). Characteristics of long-term survivors (more than 5 years) and patients without evidence of recurrence are shown in *Table 4*. Several risk factors were studied to assess their influence on survival. Significant differences in survival were observed between patients with single as opposed to multiple liver metastases (*Fig. 1*) and with patients undergoing curative surgery as opposed to palliative surgery (*Fig. 2*). Resection of single metastases was associated with actuarial survival rates of 67, 55 and 48 per cent at 1, 2 and 5 years respectively, whereas resection of multiple metastases was associated with survival rates of 55, 28 and 0 per cent ($P<0·05$). Patients who had curative operations had actuarial survival rates of 72, 59 and 52 per cent at 1, 2 and 5 years respectively, whereas those who underwent palliative operations had survival rates of 50, 25 and 0 per cent ($P<0·05$).

Patients with metachronous metastases survived longer than those with synchronous metastases, but not significantly so; resection of metachronous metastases was

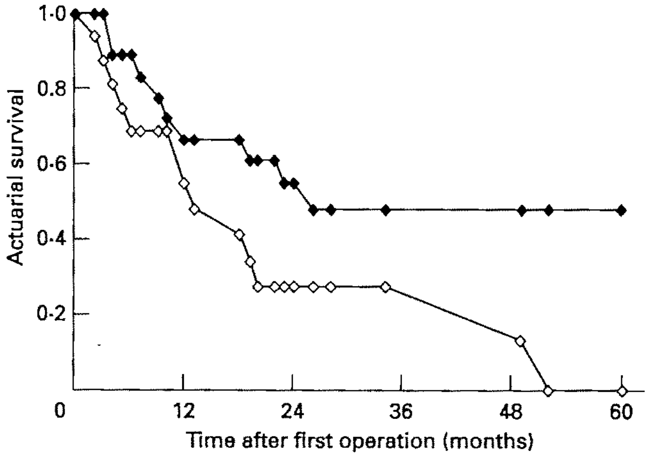

Fig. 1 Comparison of actuarial survival curves after surgery for patients with a single hepatic metastasis (◆, $n=18$) or multiple metastases (◇, $n=16$). $P<0·05$ (Mantel–Cox test)

associated with survival rates of 63, 48 and 36 per cent at 1, 2 and 5 years respectively, compared with 58, 33 and 0 per cent for resection of synchronous metastases ($P > 0{\cdot}2$). However, the length of delay between resection of the primary tumour and discovery and resection of liver metastases was strongly correlated with survival ($r = 0{\cdot}60$, $P < 0{\cdot}001$). Moreover, long-term survivors and patients alive with no evidence of disease (*Table 4*) had a significantly longer period between presentation of primary and metastatic lesions (median 96 months) than the other patients (median 18 months) ($P < 0{\cdot}0001$). Sex, age, type of hepatectomy (major *versus* minor) and amount of intraoperative blood transfused had no effect on survival.

When these figures were combined with those available in the recent literature, a total of 141 patients from this and eight other series[13–16,19–22] could be analysed. The actuarial survival rate was 70 per cent at 1 year, 52 per cent at 2 years, 42 per cent at 3 years and 19 per cent at 5 years (*Fig. 3*) with a median survival of 26 (95 per cent confidence interval 20–36) months. This large group of patients allowed evaluation of the effect of histological type on survival. Only groups of ten patients or more were assessed and compared with the remainder. Patients with a neuroendocrine primary tumour ($n = 31$) had a better survival rate (73 per cent at 1 year, 61 per cent at 2 and 5 years; $P < 0{\cdot}0001$) (*Fig. 3*), whereas patients with a gastrointestinal adenocarcinoma (gastrointestinal tract, pancreas, biliary tract; $n = 20$) had a worse outcome (45 per cent at 1 year, 15 per cent at 2 and 5 years; $P < 0{\cdot}0001$) (*Fig. 3*). The survival rate of patients with breast carcinoma was similar to that of the whole group (92 per cent at 1 year, 64 per cent at 2 years and 10 per cent at 5 years; $P > 0{\cdot}5$) (*Fig. 3*). Other groups of patients with gynaecological adenocarcinomas (ovary, fallopian tube, uterus; $n = 10$), melanoma ($n = 10$) or other sarcomas ($n = 26$) had no significant survival differences compared with the remainder (data not shown).

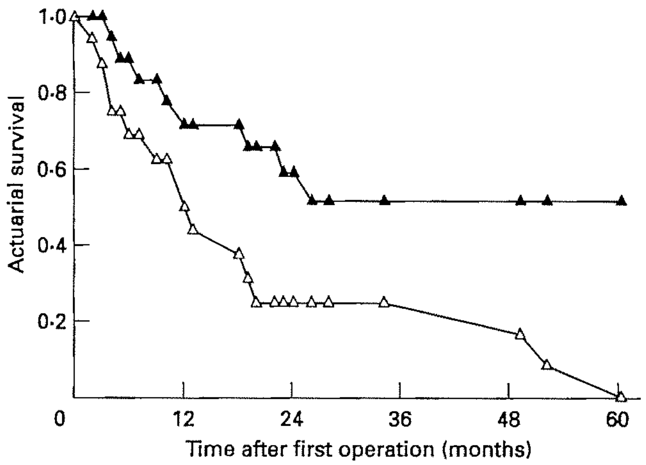

Fig. 2 Comparison of actuarial survival curves after curative surgery of hepatic metastases (▲, $n = 18$) or palliative surgery (△, $n = 16$). $P < 0{\cdot}05$ (Mantel–Cox test)

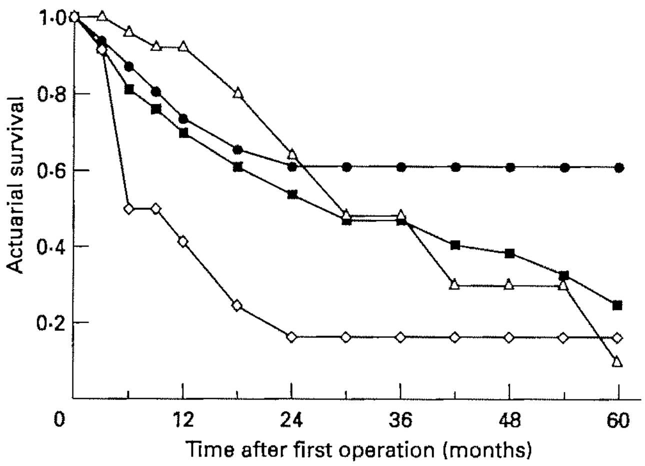

Fig. 3 Actuarial survival of 141 patients reported in the literature, who underwent resection of non-colorectal hepatic metastases (■). The survival curves of subgroups with metastases from neuroendocrine tumours (●, $n = 31$), breast carcinoma (△, $n = 25$) and digestive adenocarcinomas (◇, $n = 20$) are also plotted. These subgroups exhibited, respectively, a significantly better ($P < 0{\cdot}0001$), similar ($P > 0{\cdot}5$) and worse ($P < 0{\cdot}0001$) prognosis than the whole group (Mantel–Cox test)

Discussion

Surgical resection is the only potentially curative treatment for most metastatic cancers to the liver nowadays, even if the occasional cure occurs in a most unpredictable fashion. It can also offer significant prolongation of survival or efficient palliation of tumour-related symptoms[1–3,23]. Liver transplantation in the treatment of colorectal metastases produces poor results[1,8,24,25] and in a recent multicentre study of liver transplantation for neuroendocrine metastases a 5-year survival rate of only 36 per cent was achieved[26], compared with the figure of 61 per cent reported here.

Table 4 Characteristics of long-term survivors and patients with no evidence of recurrence

Patient no.	Sex	Age (years)	Primary tumour	Duration of follow-up (months)*	Current status
1	F	57	Gastrinoma of the pancreas	22	No evidence of disease
2	F	64	Carcinoma of the endometrium	28	No evidence of disease
3	F	27	Carcinoma of the adrenal cortex	28	No evidence of disease
4	M	42	Melanoma of the eye	49	Lost to follow-up†
5	M	77	Cystadenocarcinoma of the pancreas	70	No evidence of disease
6	M	62	Carcinoma of the ampulla of Vater	84	No evidence of disease
7	F	54	Carcinoma of the ovary	105	No evidence of disease
8	F	23	Leiomyosarcoma of the stomach	119	Alive with disease

*Since resection of metastases. †Patient had no evidence of disease at the time he was lost to follow-up

Few reports dealing exclusively with the resection of liver metastases from non-colorectal primaries are available in the surgical literature. Only a minority deal with homogeneous groups of patients with secondaries originating from the same organ, although in some of them haematogenous metastases and direct invasion are combined[19–22].

On the whole, it seems that 5-year survival rates of 15–25 per cent can be expected after resection of non-colorectal, non-Wilms liver metastases. These results are achieved, of course, for a small proportion of highly selected patients but they compare favourably with values obtained with chemotherapy alone[13,15]. With the most recent chemotherapeutic or hormonal regimens, median survival times of 3–9 months are obtained for gastric cancer[27], 1–7 months for pancreatic cancer[28] and 7–14 months for breast cancer[29,30], with no 5-year survivors. The price to pay for this improvement of survival is that of perioperative mortality and morbidity. The safety of hepatic surgery has improved tremendously in recent years, and the reported perioperative mortality rate after resection of non-colorectal liver metastases has been in the range of 0–8 per cent for the past 10 years. The present figures (perioperative mortality rate 0 per cent, 5-year survival rate 27 per cent) compare favourably with the most optimistic of the studies published previously and represent the groundwork in the case for resection of these metastases.

The presence of a single metastasis was associated with significantly better survival. Hepatic resection for a single metastasis was also found to be an indicator of favourable outcome in most available series[9,12,31], albeit not consistently[10,11]. In one study, it was demonstrated that, in patients with a single non-colorectal metastasis surrounded by satellite nodules, survival was comparable to that of patients with single and not with multiple metastases[12]. For this reason, patients with satellite nodules around a single metastasis were classified with the single metastasis group, with similar results of improved survival. However, the presence of satellite nodules around a metastasis was found to be a factor for poor prognosis in large series of resection for colorectal metastases[32].

In this study, the delay between removal of the primary tumour and liver resection seemed to play a role in the length of survival after hepatectomy, although the survival difference between patients with metachronous and synchronous metastases was not significant. This finding is not unexpected as metastatic delay obviously reflects the biological aggression of an individual tumour. In the literature, synchronicity or metachronicity of the hepatic metastasis does not appear to be a major prognostic factor. Some authors have found no differences in survival between the two groups[9,10,12], while others have found a more favourable outcome in the metachronous[11] or even in the synchronous[31] group.

Extent of surgical resection does not seem to play an important role. In one early publication[10], minor resections were associated with a better prognosis, but this was not confirmed by other studies in which major resections were associated with better survival[31] or extent of resection was not important[16,32].

Finally, the curative nature of the resection is the only unanimously accepted indicator of good prognosis, and was identified as such in this study.

Combination of survival figures with regard to histological type was possible for 141 patients from nine series including the present one. It appears that patients with neuroendocrine tumours are by far the best responders to surgical resection with survival rates in excess of 60 per cent at 5 years. This apparent success is undoubtedly related to the generally protracted course of these tumours and unequivocally justifies the use of surgical resection as part of a combined and iterative oncological–surgical approach, which may include surgical resection, with repeat hepatectomy whenever necessary, chemotherapy, chemoembolization and ethanolization[23].

On the other hand, the composite group of patients with digestive adenocarcinoma experienced a significantly worse outcome, especially in short-term survival. The few unpredictable 5-year survivors reported prevent the immediate dismissal of such patients from surgical therapy. However, they should be proposed only for surgery with clearly curative intent, in favourable cases such as when there is a single metastasis confined to one lobe of the liver and without extrahepatic involvement. This is probably also the case for the remainder of patients with non-colorectal, non-neuroendocrine secondaries in the liver and stresses the importance of performing extensive preoperative imaging studies for accurate assessment of the extension of metastatic disease and better selection of patients eligible for surgery. For the homogeneous group of patients with secondaries from breast carcinoma, survival was statistically similar to that of the whole group, but the benefit of surgical resection seems to be essentially short term as the 5-year survival rate is poor (10 per cent).

Until further advances are reached in the field of oncology, surgery will remain the only opportunity for cure for a few selected patients, whose prospects without an operation are dismal. When this is put in perspective with the great safety of hepatic surgery achieved today, it amply demonstrates the appropriateness of surgical excision of non-colorectal secondaries.

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Effects of loperamide on ileoanal pouch function

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Background Opioid analogues are used to manage increased bowel frequency in patients with an ileoanal reservoir. The aim of the study was to determine the clinical efficacy of loperamide in patients with an ileoanal reservoir and to assess its effect on pouch motility.

Methods Fourteen patients with a pouch who had normal pouch emptying and anal function were studied. Ambulatory pouch and anal motility, and stool weights, were recorded for 24 h while taking no medication and for 24 h while receiving 8 mg loperamide. In a second analysis, patients were divided on the basis of bowel frequency into those with 4 or fewer motions (good function; $n = 6$) and those with more than 6 per day (poor function; $n = 8$), to determine any differential effects of loperamide.

Results Loperamide decreased median bowel frequency (no loperamide 5·5 *versus* loperamide 4·0, $P = 0{\cdot}03$) and 24-h stool weight (610 g *versus* 413 g, $P = 0{\cdot}03$) but not individual stool weights. Patients with poor function had both higher bowel frequency (8·0 *versus* 3·5 per 24 h, $P = 0{\cdot}004$) and higher stool weight (728 g *versus* 430 g, $P = 0{\cdot}05$) with no treatment than those with good function. High-amplitude pouch pressure waves were greater in number before defaecation in patients with poor function and did not decrease with loperamide, in contrast to patients with good function. Pouch baseline pressure decreased after defaecation to a similar extent in both groups and was not affected by loperamide.

Conclusion Loperamide 8 mg per day reduces bowel frequency by reducing total stool weight, not individual stool weights. In patients with good function it also affects pouch motility. High bowel frequency is associated with increased pouch high-pressure waves.

Restorative proctocolectomy is now a well established procedure in the treatment of ulcerative colitis and familial adenomatous polyposis. Most patients have good function with a bowel frequency of six or fewer motions per 24 h, the ability to defer defaecation and good continence[1,2]. However, a small proportion of patients have chronically impaired function, with increased bowel frequency, urgency and incontinence. This may be due to anatomical factors, such as sphincter damage or small reservoir capacity, to inflammation in the pouch, or to a disturbance of pouch motility in the presence of an uninflamed anatomically satisfactory pouch. The management of patients with poor pouch function depends on identifying underlying causative factors, but the use of opioids or their analogues often appears to provide a useful therapeutic approach.

The clinical usefulness of loperamide has been established in a wide range of chronic diarrhoeal states, such as short bowel syndrome, ileostomy dysfunction, and diarrhoea following hemicolectomy[3]. Its benefit has been demonstrated in patients with a straight ileoanal anastomosis[4], and its efficacy has been assessed in patients with an ileoanal reservoir[5] in the clinical setting, but not using long-term ambulatory manometry.

The first aim, therefore, was to determine whether loperamide, a safe and normally efficacious opioid analogue, is clinically helpful in patients with an ileoanal pouch. The second aim was to determine whether any therapeutic benefit is due to a reduction in stool frequency or to the amount of stool passed. Thirdly, the effect of the drug on pouch motility was assessed. Lastly, the effects of loperamide in patients with high *versus* low bowel frequency were studied to determine any difference.

Patients and methods

Patients

Fourteen patients (nine men and five women of median age 46 (range 22–57) years) were studied. The median time since closure of the ileostomy was 5·1 (range 0·8–11·7) years. There were nine W, four J and one S pouch, all with a transanal mucosectomy and hand-sewn ileoanal anastomosis. The original diagnosis was ulcerative colitis in ten patients and familial adenomatous polyposis in four. Patients with a stricture at the ileoanal anastomosis, poor pouch emptying (clinically or on proctography) or a small pouch on contrast radiography were excluded. Other reasons for high frequency of defaecation such as enteric infection, pancreatic insufficiency, coeliac disease and malabsorption of other causes were excluded.

Five patients with a previous diagnosis of ulcerative colitis had chronic relapsing pouchitis. Four of these five patients were taking metronidazole intermittently, and one was receiving it continuously. Pouchitis was defined as the presence of the combination of endoscopic inflammation and histological acute inflammation[6]. None of these patients had an acute episode of pouchitis at the time of the study but all had an increased frequency of defaecation. All patients had normal anal sphincter function.

To analyse any differential effects of loperamide, patients were divided in two groups: patients with low bowel frequency (4 or fewer per 24 h, good function) and those with high bowel frequency (more than 6 per 24 h, poor function).

The study was approved by the local ethics committee and all participants gave written informed consent.

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Patient assessment

All patients had clinical examination of the pouch including rigid endoscopy and biopsy at least 1 week before the study. All drugs were stopped at least 48 h before commencement of the study.

Before the study physiological tests of anal and pouch function were carried out as published previously[7]. These included anal manometry, electrosensory testing of the anal canal, and a study of pouch compliance and the motor response to distension (pouchmetrography)[8].

Equipment

A solid-state catheter with two pressure transducers spaced 10 cm apart (Gaeltec, Isle of Skye, UK), connected to a solid-state recorder, was used to record pouch and anal pressure activity, according to previously published techniques[9].

Patients were hospitalized and after an overnight fast emptied the pouch before catheter insertion. The catheter was blindly inserted transanally and the distal sensor positioned in the mid-anal canal. Positioning of the anal sensor in the high-pressure zone was facilitated by a real-time pressure display on the recording box. The catheter was then taped to the perianal skin.

During the study participants were freely mobile within the hospital. Patients kept a written diary of their activities in addition to recording events (eating, drinking, sleeping, urge to defaecate, start and end of defaecation) using specific buttons on the portable recorder. The perineal area was frequently checked to keep the probe in correct position.

Stored data were downloaded to a personal computer (IBM PS/2) as required and recording was continued immediately thereafter.

Study design

Two successive 24-h periods starting at 08.00 hours were studied. Subjects were fasted for 4 h until 12 noon on each day. The same standardized meals of lunch, dinner and two snacks, to a total of 7910 kJ (1890 kcal), were consumed on both study days. Fluids were allowed *ad libitum* after lunch on the first day until 06.00 hours on the second study day when fasting was resumed.

No drugs were given on the first study day, but on the second day at 08.00, 12.00, 16.00 and 20.00 hours patients ingested one capsule containing 2 mg loperamide (Imodium; Janssen, Beerse, Belgium). All bowel motions were collected and weighed immediately for the 48-h duration of the study.

Analysis of motility recordings

All analyses were performed using a computer program (MMS; Enshede, The Netherlands). All results were checked visually on the computer screen by two investigators. The baseline pouch pressure was determined for the 15 min before and after defaecation. In addition high-pressure waves, defined as single pouch contractions with an amplitude of 20 cmH$_2$O or greater were identified for each study, and their time of occurrence and amplitude were measured.

Pouch motor complexes, defined as rhythmic pressure rises with a frequency of 6–12 per min and lasting from 30 s up to 120 min, were identified, and the time of their start and duration recorded. Their numbers were expressed relative to 24 h for each study day and the median frequency and amplitude were calculated.

Comparisons were made between the two study days. In the second analysis, comparisons were made within each group of patients, and between the two groups of patients, within the first and then the second study days.

Comparisons were made for the following parameters: (1) the median baseline pouch pressure for 15 min before and after defaecation in each patient over a 24-h study day; (2) the median difference within each patient between the pressures before and after defaecation for each 24-h study day; (3) the median number of high-amplitude pressure waves per hour within each patient for each study day; (4) the median amplitude within each patient of all high-pressure waves within each study day; (5) the median number of high-pressure waves in each patient before defaecation on both study days; (6) features of pouch rhythmic activity.

Results

All patients completed the study successfully. A median of 44 (range 35–48) h of recording time was analysed.

Functional characteristics and anal and pouch physiological tests

All patients had a maximum resting anal pressure and squeeze pressure within the normal range. Anal manometry, anal electrosensitivity and pouch threshold, urge and maximum tolerated volumes did not differ significantly between the two patient groups. However, median (range) pouch compliance was significantly lower in patients with poor function (good function 16·3 (4·3–68·8) ml/cmH$_2$O *versus* poor function 7·9 (1·5–27·5) ml/cmH$_2$O; $P = 0{\cdot}03$, Mann–Whitney U test).

Effects of loperamide on defaecation frequency and stool output

Loperamide caused a significant reduction in the 24-h stool output in all patients, and for each of the two groups of patients when considered individually (*Table 1*). To determine whether this reduction occurred to a similar extent in patients with a low or high initial output, the output on the no-treatment and loperamide treatment days was expressed as a ratio and plotted against the initial no-treatment output. This showed that patients with

Table 1 Effects of loperamide on bowel frequency and stool weight

	All patients ($n = 14$)	Good function ($n = 6$)	Poor function ($n = 8$)
Total stool weight in 24 h			
No treatment	610 (85–1315)‡	430 (85–840)§	728 (179–1315)*§
Loperamide	413 (100–1005)	348 (100–700)	443 (129–1005)
No. of defaecations in 24 h			
No treatment	5·5 (2–12)‡	3·5 (2–5)	8 (4–12)†
Loperamide	4 (1–10)	2·5 (1–4)	7 (3–10)

Values are median (range). *$P = 0{\cdot}05$, †$P = 0{\cdot}004$ *versus* good function (Mann–Whitney U test); ‡$P = 0{\cdot}03$, §$P = 0{\cdot}04$ *versus* loperamide (Wilcoxon signed rank test) a low and high initial output experienced a proportionately similar reduction ($R^2 = 0{\cdot}54$, $P = 0{\cdot}11$) in output as a result of the drug. The median reduction in stool weight over 24 h was 125 g, equalling a median of 24 per cent of the output.

Considering all patients together, loperamide also caused a significant reduction in the 24-h bowel frequency. Considered separately, both groups of patients experienced a reduction in bowel frequency while taking loperamide, but this was not statistically significant (*Table 1*). This was likely to relate to the range of bowel frequency and number of patients in each group.

There were 156 stool samples passed in total, 94 on day 1 and 62 on day 2. This comprised 21 and 16 from patients with good function, and 73 and 46 in the poor function group, on days 1 and 2 respectively. For the purpose of comparison, the mean weight for individual stools was determined for each patient for each study day. On no medication, the mean weight of individual bowel actions was similar in both patient groups (good function 116 g *versus* poor function 110 g, median, $P = 0{\cdot}9$). Loperamide did not significantly change the weight of individual stools, when considering all patients together or patients with good and poor function separately.

During the first study day, while taking no medication, there was a significant difference between the two patient groups for the total 24-h stool weight. Patients with high frequency had a higher stool weight (*Table 1*). In addition there was a positive correlation between total stool output and stool frequency ($R^2 = 0{\cdot}44$, $P = 0{\cdot}044$).

Table 2 Ileoanal pouch motility when taking and not taking loperamide

	All patients ($n = 14$)	Good function ($n = 6$)	Poor function ($n = 8$)
HPWs per h			
Day 1	8	7	13*
Day 2	9	6	11
Peak pressure of HPWs (cmH_2O)			
Day 1	36	34	37
Day 2	36	37	35
HPWs within 30 min before defaecation			
Day 1	9	7	10
Day 2	9	5	10‡
HPWs within 15 min before defaecation			
Day 1	5	4	6
Day 2	6	2	7†
Pouch baseline pressure within 15 min before defaecation (cmH_2O)			
Day 1	26§¶	26¶	26††
Day 2	30¶	31#	28**
Pouch baseline pressure within 15 min after defaecation (cmH_2O)			
Day 1	20	20	20
Day 2	22	26	19

Values are median. HPW, high-pressure wave. *$P = 0{\cdot}03$, †$P = 0{\cdot}04$, ‡$P = 0{\cdot}05$ *versus* good function (Mann–Whitney *U* test); §$P = 0{\cdot}02$ *versus* day 2 before defaecation; #$P = 0{\cdot}001$, ¶$P = 0{\cdot}01$, **$P = 0{\cdot}02$, ††$P = 0{\cdot}03$ *versus* after defaecation (Wilcoxon signed rank test). Comparison of the magnitude of difference in pouch baseline pressure before and after defaecation between study days gave $P = 0{\cdot}46$ for patients with good function and $P = 0{\cdot}26$ for those with poor function (Wilcoxon signed rank test)

Motility analysis

The median baseline pouch pressure, for the 15 min both before and after defaecation, was similar for both patient groups. The pressure was marginally higher before defaecation for the groups combined when taking loperamide.

After defaecation the median pouch pressure decreased significantly in both patient groups, when taking no medication and when receiving loperamide. The magnitude of this difference was similar for both patient groups and on both study days (*Table 2*).

When taking no medication, patients with high bowel frequency had significantly more high-pressure waves per hour than those with low frequency. This difference diminished with loperamide, although the patients with high bowel frequency still had a higher number of pressure waves than those with low frequency (*Table 2*).

On the first study day, the median number of high-pressure waves both for the 30- and 15-min time intervals before defaecation was greater in patients with poor function (*P* not significant). With loperamide, patients with low frequency, but not those with high frequency, experienced a reduction in the number of high-pressure waves before defaecation.

The median amplitude for each patient of high-pressure waves was similar between the two patient groups and between the two study days (*Table 2*).

Pouch motor complexes were identified in ten patients (four with good and six with poor function). There was no difference in the number of complexes over 24 h, median frequency per minute, amplitude or duration, either between the two patient groups or between the two study days within a patient group.

Discussion

Loperamide was synthesized in 1969 and designed to improve the antidiarrhoeal activity shown by diphenoxylate. At oral antidiarrhoeal doses, about 80 per cent of administered loperamide is confined to the gastrointestinal tract and the enterohepatic circulation[10]. Within the intestinal wall, loperamide concentrates in the longitudinal muscle and myenteric plexus[11] and therefore exhibits few systemic effects[12]. It shows both antimotility and antisecretory effects in the human small bowel and increases the orocaecal transit time in healthy subjects[13], patients with irritable bowel syndrome and diarrhoea[14], and those with postvagotomy diarrhoea[15]. Its clinical usefulness has been established in a variety of conditions including ileostomy dysfunction[16], diarrhoea following right hemicolectomy[3], in patients with a straight ileoanal anastomosis[4] and also in those with an ileoanal pouch[5]. This study demonstrated that clinical function was improved, with a reduced bowel frequency and improved night-time continence, while pouch volume and contractility were not affected.

The aims of the present study were twofold: first, to assess the clinical usefulness of loperamide in the management of patients with high bowel frequency following restorative proctocolectomy and, second, to characterize and quantify its effects on pouch motility.

Although the ideal study would have involved a placebo-controlled design, the methodology chosen enabled the study to be undertaken with only one probe insertion. If the study had been placebo-controlled, with some patients receiving active drug first, then it is possible that the drug might still have been exerting some effect on the second study day in these patients. In the present study patients acted as their own controls. The differences were consistent and marked, and therefore unlikely to relate to a placebo effect.

Patients included in the study had poor clinical function due to a high frequency and were thought to have a disturbance of motility or pouchitis. Patients with an anatomical pouch or sphincter problem were excluded. Despite satisfactory radiological pouch size and similar threshold, urge and maximum tolerated volumes, pouch compliance was lower in patients with high bowel frequency. This has also been observed previously[8,17,18] and is likely to relate largely to the history of pouchitis in five of the eight patients with high bowel frequency. In addition to abnormal compliance, patients with poor function in this study had higher 24-h stool weight than those with good function.

Loperamide reduced the 24-h stool output by one-quarter in all patients. This resulted in a decreased bowel frequency rather than a reduction in the weight of individual stools. The magnitude of the reduction in stool weight was similar for patients with smaller and larger outputs, a finding at variance with another study in patients with a straight ileoanal anastomosis[4]. The difference may relate to differences in anatomy or to the higher loperamide dose used in the other study[4]. The reduction in total stool weight was also similar for both patient groups.

Patients with high bowel frequency did not pass smaller motions than those with good function. The weight or volume of individual stools will depend on the underlying condition in patients with high bowel frequency. In a previous study[19] patients with poor function but without pouchitis had a smaller individual stool volume than those with good function, and their pouch sensitivity volumes also differed. In the present study the cause of high frequency was different, and often involved pouchitis. This is likely to account for the increased total stool weight in the present patients with poor function.

Loperamide did not affect the weight of individual stools passed. The reduction in 24-h output and frequency is likely to be due to an effect on both motility and absorption. Effects of the drug on motor function were documented in the pouch, but effects on motor function in the proximal small bowel and effects on secretion in the pouch may also occur. The lack of effect on baseline pressure suggests that loperamide did not have a major effect on pouch tone, which is in accordance with the findings of another study[5], although barostat measurements would be a more precise way of establishing this. The drug was also unlikely to have mediated its effect by changing anal tone.

In this study pouch pressure fell after defaecation. In a previous study of patients with a pouch who had incontinence[20], pouch pressure did not fall to the same degree as in patients with good function, suggesting a failure of evacuation.

High-pressure waves are observed in both continent ileostomies (Kock) and pelvic ileal pouches, and have been related to function. As they tend to cluster before defaecation[21] and decrease after defaecation, their occurrence has been related to pouch filling[22,23]. They are associated with a desire to empty and a sense of urgency[17]. There is a considerable range in their reported mean frequency, from 4 to 12 per hour in long-term ambulatory motility studies[21,23,24].

In this study, the mean frequency of high-pressure waves on the first study day was significantly greater in patients with high bowel frequency. Loperamide caused a reduction in their frequency in all patients, and may therefore act partially by reducing the response of the pouch to filling. Ferrara and colleagues[24] found a similar incidence in the number of high-pressure waves when studying patients with good and poor function, but their patients with poor function had incontinence, suggesting a different reason for poor function.

High-pressure waves in the 30 min before defaecation were decreased by loperamide only in patients with good function. The threshold for initiation of these motor events would therefore appear to be lower in patients with good function, and more susceptible to pharmacological suppression.

In summary, patients with poor pouch function, but normal anal function, including those with chronic pouchitis, have an increased total stool output with normal individual stool weights. They have an increased number of high-pressure waves before defaecation. Loperamide decreases the stool frequency by reducing total stool weight, and not the weight of individual stools. It also decreases the number of high-pressure waves in patients with good function. The effects of the drug on function in patients with an ileoanal reservoir relate to both motility and absorption.

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Third-degree obstetric perineal tear: long-term clinical and functional results after primary repair

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Background This study was designed to investigate the long-term clinical and anorectal functional results after primary repair of a third-degree obstetrical perineal rupture.

Methods One hundred and fifty-six consecutive women who had a primary repair of a third-degree perineal rupture were sent a questionnaire and asked to undergo anorectal function testing (anal manometry, anorectal sensitivity, anal endosonography and pudendal nerve terminal motor latency (PNTML))

Results Some 117 women (75 per cent) responded. Anal incontinence was present in 47 women (40 per cent); however, in most cases only mild symptoms were present. In 40 women additional anorectal function tests were performed and compared with findings in normal controls. Mean(s.d.) maximum squeeze pressure (31(15) *versus* 63(17) mmHg, $P < 0{\cdot}001$) was decreased and first sensation to filling of the rectum (88(47) *versus* 66(33) ml, $P = 0{\cdot}03$) and anal mucosal electrosensitivity (4·7(1·7) *versus* 2·5(0·8) mA, $P = 0{\cdot}003$) were increased compared with values in normal controls. In 35 women (88 per cent) a sphincter defect was found with anal endosonography. Factors related to anal incontinence were the presence of a combined anal sphincter defect (relative risk (RR) 1·7 (95 per cent confidence interval (c.i.) 1·1–2·8)) or subsequent vaginal delivery (RR 1·6 (95 per cent c.i. 1·1–2·5)).

Conclusion Anal incontinence prevails in 40 per cent of women 5 years after primary repair of a third-degree perineal rupture. The presence of a combined sphincter defect or subsequent vaginal delivery increase the risk of anal incontinence.

Anal incontinence occurs in approximately 2·2 per cent of the general Western population, especially in women[1]. Many women with anal incontinence have a history of one or more difficult vaginal deliveries. After a third-degree perineal tear, which involves rupture of the anal sphincters and occurs in about 0·4–5 per cent of vaginal deliveries[2–7], anal incontinence rates from 19–58 per cent within several months after the rupture[2,4,8–12] to 7–42 per cent after several years[8,9,11] have been reported. These complaints can have serious consequences for the social, psychological and sexual life of those affected. The exact cause of anal incontinence after third-degree perineal tear is not clear. Both sphincter rupture and pudendal nerve damage are considered pathophysiological factors[4,13–15]. Anal endosonography, which provides clear images of the anal sphincters, is advocated in the assessment of anal incontinence[16,17], as well as other anorectal function tests, and might help insight to be gained into the pathophysiology of anal incontinence after third-degree perineal tear.

The aim of this study was to investigate long-term clinical and anorectal functional results after primary repair of a third-degree obstetrical perineal rupture.

Patients and methods

Between 1985 and 1994, 156 women (approximately 1·8 per cent of all vaginal deliveries[5]) with a mean age of 31 (range 18–43) years underwent primary repair of a third-degree obstetric perineal tear (anal sphincter tear) in the authors' hospital. A complete third-degree obstetric anal sphincter tear was defined as a rupture of the perineum with total separation of the anal sphincters, with or without a breach of the anal epithelium[3,4]. When some fibres of the anal sphincter remained intact, the third-degree tear was defined as incomplete[3]. All tears were confirmed and sutured by a staff gynaecologist. The torn ends of the anal sphincters, which were retracted, were identified and approximated with interrupted or 'figure of 8' sutures of polyglactin[18]. The vaginal mucosa, perineal muscles and skin were then repaired as in routine episiotomy. Postoperative complications included wound infection in four patients and anovaginal fistula in two. Nineteen women were lost to follow-up. The remaining 137 women were sent a questionnaire 1–10 years after the anal sphincter tear (mean follow-up 4·7 years), containing questions about anal incontinence, urinary incontinence, vaginal flatus and dyspareunia. The severity of anal incontinence was assessed by a 100-mm visual analogue scale (VAS), the descriptions at each end being 'no distress' and 'distress couldn't be worse'.

In addition, all women who were sent a questionnaire were asked to undergo anorectal function tests. The study was approved by the medical ethics committee.

Anorectal function tests

Anal endosonography. Anal endosonography was performed with a Diagnostic Ultrasound System (type 3535; Brüel and Kjër, Naerum, Denmark) with a 7-MHz rotating endoprobe (type 1850, focal range 2–4·5 cm) covered by a water-filled hard sonolucent cone (diameter 1·7 cm), producing a 360° view of the anal canal. Serial images of the anal sphincters were obtained both transvaginally[19] and transanally. Mean internal and external

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anal sphincter thicknesses were assessed with a calliper (electronically or manually). *Fig. 1* shows an example of a normal endosonogram. A defect was defined as discontinuity in the endosonographic appearance of the internal (hypoechoic) or external (hyperechoic) sphincter and noted clockwise (*Figs 2* and *3*).

Anal manometry. Anal manometry was performed with the patient lying in the left lateral position with a solid-state catheter 2 mm in diameter with two microtip transducers (Gaeltec, Dunvegan, UK)[20]. The maximum basal pressure (MBP) and the maximum squeeze pressure (MSP; the maximum increase above the basal pressure at voluntary contraction) were registered. The sphincter length (SL) was calculated.

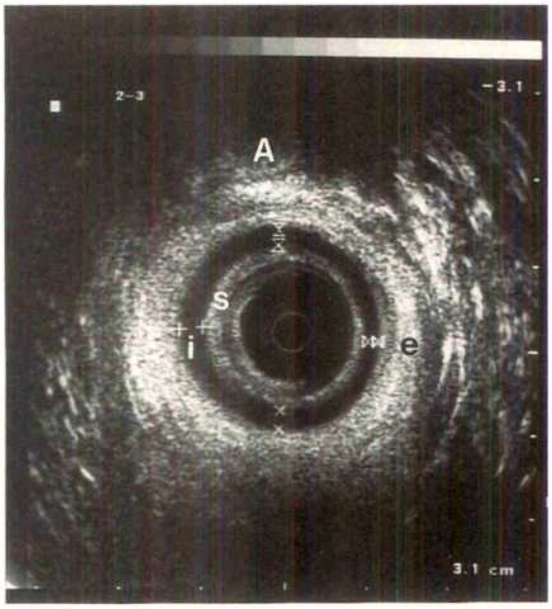

Fig. 1 Normal anal endosonogram, showing an intact internal anal sphincter (i) and external anal sphincter (e). s, Submucosa; A, anterior

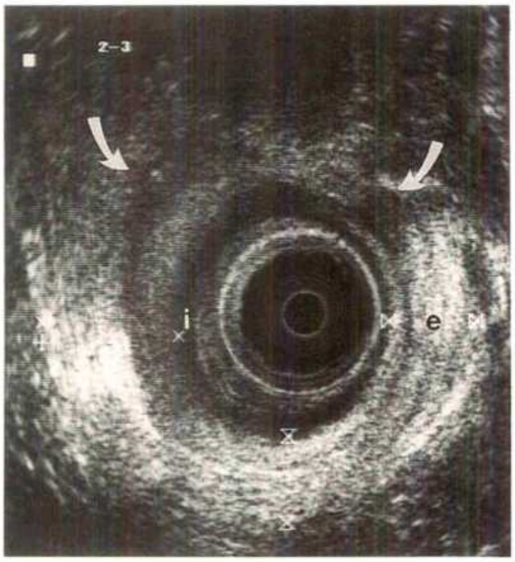

Fig. 2 Anal endosonogram showing a defect of the external anal sphincter (e) (between the arrows). The internal anal sphincter (i) has remained intact

Rectal sensitivity. A catheter (MTC; Dräger, Best, The Netherlands) with a microtip transducer mounted on to a terminal rectal balloon was used[20]. The catheter was introduced into the rectum of the patient and the balloon was filled with 100 ml water per min. Patients were asked to indicate the experience of first sensation of filling of the rectum (FS), normal urge to defaecate (urge) and of maximum tolerated volume (MTV).

Anal mucosal electrosensitivity. A probe with two small electrodes was introduced into the anal canal. A constant current (square wave stimulus 100 ms, 5 pulses per second) was increased gradually from 1 to 20 mA until the threshold of sensation was indicated by the patient[21].

Pudendal nerve terminal motor latency. This was measured in 37 women with a specially constructed finger stall[22] with stimulating electrodes mounted at the tip and recording electrodes at the base. The device was placed on the glove of the

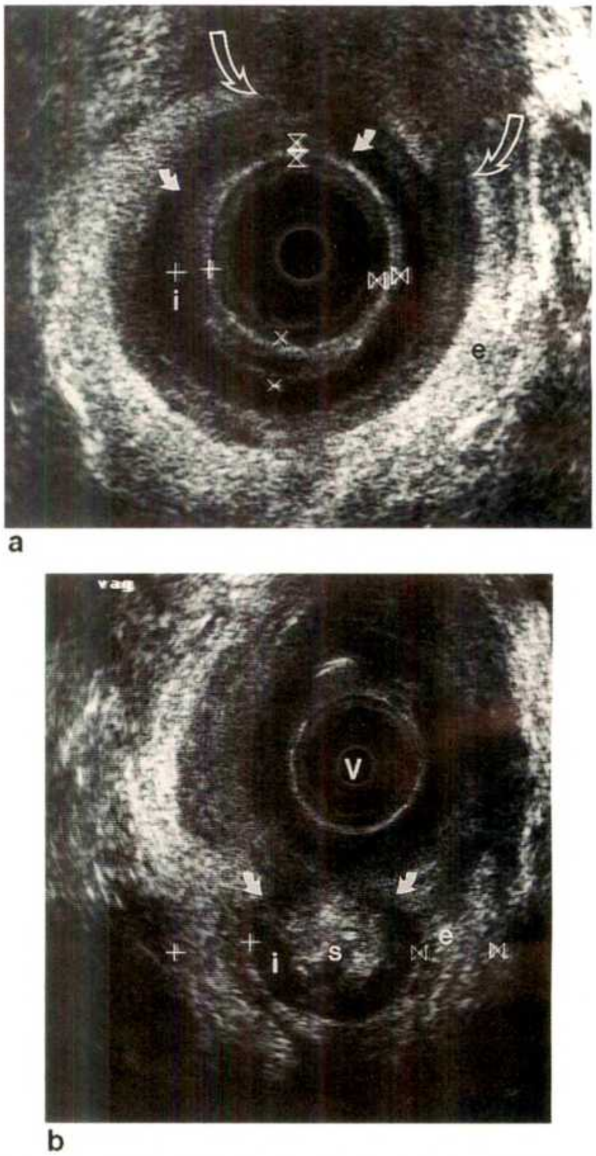

Fig. 3 a Anal endosonogram showing a defect of both the internal anal sphincter (i) (small arrows) and external anal sphincter (e) (open arrows). **b** The same defect with vaginal endosonography. V, probe in the vagina; i, internal anal sphincter; e, external anal sphincter; s, submucosa index finger of the investigator (R.L.M.S.) and introduced into the anal canal. The pudendal nerve of each side was stimulated with a supramaximal stimulus 0·05 ms in duration. The deflection of the baseline was called the pudendal nerve terminal motor latency (PNTML). The PNTML of both the right and left side was measured and compared with normal mean(s.d.)values (1·94(0·3) ms). PNTML greater than 2·25 ms was considered abnormal.

Statistical analysis

Summary statistics were expressed as mean(s.d.). The relation between complaints and anorectal function test results was assessed with multiple linear regression analysis or the Mantel–Haenszel χ^2 test for trends. Comparisons between patients and controls (corrected for age and parity) and between continent and incontinent women with anal sphincter tear were made with analysis of variance (or the Kruskal–Wallis test in case of non-parametric data).

Results

Questionnaire

General data and complaints are shown in *Table 1*. There were 117 responders (75 per cent). Thirty-eight women (32 per cent) had a complete and 79 (68 per cent) an incomplete rupture. Twelve complete ruptures were associated with mucosal injury of the anorectum.

Sixty-five women (56 per cent) had one or more perineal complaints, while 52 (44 per cent) were symptom-free. Although a large proportion of women reported anal incontinence, most of them had infrequent involuntary loss of faeces or flatus (23 per cent on a daily basis, 26 per cent on a weekly basis and 51 per cent on a monthly basis). This was reflected by the low mean(s.d.) VAS of severity of the anal incontinence (2·0(2·5) on a scale of 0–10). Consequently only two women decided to undergo anterior sphincter repair after the study.

Forty-three of 110 women had a subsequent delivery (unknown in seven women). The rate of anal incontinence was higher in these women (24 (56 per cent) of 43) than in those who did not subsequently deliver (23 (34 per cent) of 67 women; relative risk (RR) 1·6 (95 per cent confidence interval (c.i.) 1·1–2·5)).

Rectal mucosa injury showed a tendency to a higher frequency of anal incontinence (58 *versus* 38 per cent, $P = 0·22$).

Anorectal function tests

Forty women (34 per cent of the responders) agreed to undergo anorectal function testing. These women did not differ from the whole group with regard to age, parity or length of follow-up. Although they tended to have more complaints than women who refused to undergo anorectal function testing, the severity of the ruptures was not significantly greater (*Table 1*). Twenty-four women (60 per cent) had anal incontinence. Twelve women (30 per cent) had no perineal complaints at all. The remaining four women had other perineal complaints such as dyspareunia or urinary incontinence. Comparisons were made both with normal controls (statistically corrected for age and parity) and between continent and incontinent women with anal sphincter tear (*Tables 2* and *3*).

Table 2 shows data for anal manometry and anorectal sensitivity measurement. MSP was decreased, and FS and anal sensitivity were increased compared with normal controls. Of the 40 women with anal sphincter tear, no differences could be found between incontinent and continent women with respect to anal pressures or anal and rectal sensitivity.

With anal endosonography, sphincter defects were detected in 35 women (88 per cent) (*Table 3*). Twenty-three women had an external sphincter defect and 12 a combined internal and external sphincter defect. No isolated internal sphincter defects were observed. All

Table 1 General data and complaints

	All women ($n = 117$)	Questionnaire ($n = 77$)	Questionnaire and manometry ($n = 40$)	P†
General data				
Mean (range) age (years)	31 (21–43)	31 (21–41)	32 (23–43)	0·18
Mean (range) follow-up (years)	4·7 (0·8–11·3)	4·8 (0·8–11·3)	4·6 (1·6–10·8)	0·69
Mean (range) parity	1·8 (1–4)	1·8 (1–4)	1·8 (1–4)	1·00
Severity of rupture				
Incomplete third degree	79 (68)	48 (62)	31 (78)	0·14
Complete third degree	38 (32)	29 (38)	9 (22)	0·14
Rectal mucosa involved	12 (10)	9 (12)	3 (8)	0·75
Faecal symptoms				
Incontinence	47 (40)	23 (30)	24 (60)	0·003
Unnoticed	3	3	0	
Urge	15	5	10	
Diarrhoea	6	2	4	
Flatus	23	13	10	
Soiling	8 (7)	4 (5)	4 (10)	0·44
VAS*	2·0(2·5)	1·6(2·5)	2·4(2·6)	
Other symptoms				
Urinary incontinence	38 (32)	20 (26)	18 (45)	0·06
Dyspareunia	16 (14)	10 (13)	6 (25)	0·78
Annoying vaginal flatus	11 (9)	4 (5)	7 (18)	0·04

Values in parentheses are percentages unless stated otherwise. *Mean(s.d.) visual analogue score (inconvenience, 1–10). †Statistical comparisons were made between women who underwent manometry ($n = 40$) and those who responded only by questionnaires ($n = 77$) (Kruskal–Wallis test)

Table 2 Anal manometry and anorectal sensitivity

		Anal sphincter tear		
	Normal ($n = 12$)	All ($n = 40$)	Incontinent ($n = 24$)	Continent ($n = 16$)
Manometry				
MBP (mmHg)	57(11)	46(12)	47(13)	46(12)
MSP (mmHg)	63(17)	31(15)*	29(14)	33(16)
SL (cm)	3·4(0·9)	3·6(1·0)	3·6(1·0)	3·6(0·9)
Rectal sensitivity				
FS volume (ml)	66(33)	88(47)†	87(46)	90(50)
FS pressure (mmHg)	22(11)	22(10)	20(10)	25(11)
Urge volume (ml)	160(65)	164(62)	164(66)	164(59)
Urge pressure (mmHg)	28(17)	26(11)	25(10)	28(12)
MTV (ml)	219(79)	220(77)	212(76)	233(80)
MTP (mmHg)	39(20)	25(12)	34(12)	39(13)
Anal sensitivity (mA)	2·5(0·8)	4·7(1·7)‡	5·0(1·6)	4·1(1·7)

Values are mean(s.d.). MBP, maximum basal pressure; MSP, maximum squeeze pressure; SL, sphincter length; FS, first sensation of filling of the rectum; MTV, maximum tolerated volume; MTP, maximum tolerated pressure. $^*P < 0\cdot001$, $^\dagger P = 0\cdot03$, $^\ddagger P = 0\cdot003$ *versus* normal (Kruskal–Wallis test)

sphincter defects were confirmed by vaginal endosonography. In both continent and incontinent women a high number of external sphincter defects was found. However, incontinent women more frequently had a combined internal–external sphincter defect (RR 1·7 (95 per cent c.i. 1·1–2·8)). The size of both internal and external sphincter defects was equal in both groups. Not having a sphincter defect did not imply absence of anal incontinence. Four of five women with intact sphincters reported anal incontinence. PNTML was not known in one woman and was increased in another. In the remaining two women all anorectal function test results were normal. However, they experienced faecal incontinence less than once a month for diarrhoea, which can be considered as almost normal. VAS scores in these women were very low (less than 1).

Internal and external sphincter thickness was not different between continent and incontinent women.

PNTML was increased (greater than 2·25 ms) in five women (12 per cent). However, in the whole group PNTML was similar to that in normal controls (PNTML right, 1·8(0·3) *versus* 1·9(0·2) ms, $P = 0\cdot35$; PNTML left, 1·7(0·3) *versus* 1·9(0·2) ms, $P = 0\cdot07$) and was no different in continent and incontinent women with anal sphincter tear (PNTML right, 1·9(0·4) *versus* 1·8(0·2) ms, $P = 0\cdot32$; PNTML left, 1·8(0·5) *versus* 1·7(0·2) ms, $P = 0\cdot32$).

Table 3 Anal endosonography: sphincter defects and sphincter thickness

		Anal sphincter tear		
	Normal ($n = 12$)	All ($n = 40$)	Incontinent ($n = 24$)	Continent ($n = 16$)
No. of defects				
Internal sphincter	0	0	0	0
External sphincter	2	23	10	13
Both sphincters	0	12	10	2
Defect size (h)*				
Internal sphincter	—	2·7(1·2)	2·8(1·2)	2·0(0·7)
External sphincter	—	2·3(1·3)	2·1(1·3)	2·6(1·2)
Thickness (mm)*				
Internal sphincter	1·5(0·4)	1·6(0·4)	1·6(0·3)	1·7(0·4)
External sphincter	7·1(1·2)	6·7(1·2)	7·0(1·2)	6·3(1·0)

*Values are mean(s.d.).

Discussion

Third-degree perineal ruptures occur in 0·4–5 per cent of deliveries[2–4,6,7,23]. In the authors' hospital the frequency is 1·8 per cent[5]. It is an infrequent complication of vaginal delivery, but women affected may experience serious emotional, psychological and sexual problems.

In this study perineal complaints after primary repair of third-degree rupture were evaluated in 117 women by questionnaire. Although there might be a potential bias due to response mainly by symptomatic women, the high response rate makes such a bias unlikely. In addition, 40 of these women were investigated by anal manometry, anal endosonography and assessment of PNTML. These women were significantly more symptomatic compared with those who only responded to the questionnaire: therefore, abnormalities found during anorectal function testing might be slightly over-rated.

Symptoms, such as urinary incontinence (32 per cent), dyspareunia (14 per cent) and vaginal flatus (9 per cent) occurred frequently, but the most reported complaint was anal incontinence in 40 per cent of women. In the literature the frequency of anal incontinence after anal sphincter tear varies from 7 to 58 per cent[2,4,8–12], which is considerably higher than the reported 2·2 per cent in a general Western population (2570 households comprising 6959 individuals)[1]. The frequency may vary depending on the extent of the rupture (with or without internal anal sphincter involvement) and the technique of primary repair, although it has not been determined which technique (overlap or approximation) is superior[24,25]. In this study approximation of the sphincters was performed. Furthermore, longitudinal studies show that the frequency of anal incontinence is highest in the puerperal period and decreases after several months to years[8,9]. It seems that, after the initial trauma and subsequent surgical repair, further healing of the pelvic floor takes place slowly and thereafter stabilizes[23].

Although in this study anal pressures and anorectal sensitivity were not significantly different between continent and incontinent women with anal sphincter tear, MSP was decreased and FS and anal sensitivity were increased compared with normal controls. Besides trauma to the anal sphincters, this could also suggest neurological damage to the pudendal nerve. Pudendal nerve damage as an aetiological factor in anal incontinence after vaginal delivery has been investigated thoroughly by Snooks *et al.*[14,15,26]. They found an increased PNTML in multiparous women and after forceps extraction 48–72 h after vaginal delivery, which persisted after 2 months only in multiparous women who underwent forceps delivery[14]. They conducted a 5-year follow-up study in 14 of these multiparous women, which showed that pudendal nerve damage had persisted or even worsened[15]. They also suggested that pudendal nerve damage coexists in 60 per cent of patients with anal incontinence after external anal sphincter division[26]. However, the present authors and others[4] have observed that the PNTML is normal in most women after anal sphincter tear and is not associated with the state of continence, which suggests that the cause of anal incontinence in this population is mainly persistent mechanical injury (despite primary repair). Indeed, with anal endosonography a defect of one or both sphincters was still present in 88 per cent of women. Moreover, the presence of a combined anal sphincter defect was associated with an increased risk of anal incontinence.

Despite the large number of sphincter defects and the high anal incontinence rate in this study, most women suffered only from incontinence of flatus and the majority with incontinence for faeces had few complaints, which was reflected by the very low score of the visual analogue scale (approximately 2 on a scale of 0–10) and the fact that only two women decided to have an anterior sphincter repair after investigation. One of the reasons might be that these women, still being young, can compensate for the mechanical sphincter injury. This is sustained by the fact that a considerable number of women were fully continent despite a sphincter defect being revealed by anal endosonography, which has also been found by Nielsen *et al.*[12]. However, they may have an uncertain future, since anal incontinence is related to age, physical limitations and poor general health[1,27]. In addition, anal sphincter function has been shown to deteriorate with age[28,29]. Several factors are held responsible, such as increasing pudendal nerve latency[29,30] and fibrosis of the internal anal sphincter[31]. Evaluation of the progress of incontinence requires long-term follow-up in these women.

Another issue is whether or not to perform an elective caesarean section in subsequent deliveries, since the risk of anal incontinence is increased when there are subsequent vaginal deliveries after anal sphincter tear (RR 1·6 (95 per cent c.i. 1·1–2·5)). These results are in accord with the findings of Bek and Laurberg[8], who found an even higher relative risk of 8·7 (95 per cent c.i. 1·9–39). In the present authors' view, all women who have sustained anal sphincter tear should be evaluated by anal endosonography and anal manometry in the case of a subsequent delivery. In the presence of a large or combined sphincter defect, low anal pressures or complaints of faecal incontinence, an elective caesarean section should be considered.

In conclusion, faecal incontinence occurs frequently, but does not torment the majority of patients several years after sustaining an anal sphincter tear. Although MSP is decreased and FS and anal sensitivity are increased compared with normal controls, there is no association of these factors with anal incontinence. Subsequent vaginal deliveries and the presence of a combined internal and external sphincter defect are associated with an increased risk of anal incontinence. Obstetricians should consider offering these women an elective caesarean section for subsequent deliveries.

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Laparotomy and laparoscopy differentially accelerate experimental flank tumour growth

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Background Surgery depresses host tumoricidal activity and may increase tumour growth. This study compared the effects of laparoscopy with laparotomy on extraperitoneal tumour growth and immune function in a murine model.

Methods C57BL/6 female mice aged 8–10 weeks had tumours induced in the right flank ($n = 45$) and were randomized to undergo halothane anaesthesia only, laparoscopy or laparotomy. Flank tumour volume was assessed over 10 days. A second group of animals ($n = 540$) were randomized to undergo the same procedures and killed at 24, 48 and 96 h. Splenocytes were harvested for natural killer (NK) cell and lymphokine activated killer (LAK) cell cytotoxicity studies.

Results There was a significant increase in flank tumour growth in the first 48 h after laparotomy and laparoscopy compared with controls ($P < 0\cdot01$). By 96 h the difference was only significant in the laparotomy group ($P < 0\cdot01$). Both NK and LAK cell cytotoxicities were suppressed significantly ($P \leq 0\cdot03$) from 24 h up to 96 h following laparotomy compared with control and laparoscopy groups. There was also a significant suppression in the laparoscopy group compared with controls in the first 48 h after operation ($P \leq 0\cdot02$).

Conclusion Extraperitoneal tumour growth was significantly accelerated after laparotomy and correlated with significantly suppressed NK and LAK cytotoxicity for at least 4 days after operation. Laparoscopy had a shorter, less profound effect on tumour growth and immune function.

Observations that local or distant metastatic growth is increased after surgery are well known. This led to investigation of the relationship between operative stress and tumour growth, and it is now recognized that surgery results in decreased host resistance[1]. The precise mechanism underlying the relationship between the effect of surgical and anaesthetic stress on primary tumour growth, the recurrence of tumours and the proliferation of distant metastases remains unknown.

Berti Riboli and colleagues[2] demonstrated that all 100 patients who had a laparotomy experienced postoperative immunosuppression. This was detected from the first day, peaked by the third day after operation and was more severe and prolonged in patients with cancer. Patients with advanced malignancy already suffer from depressed immune function[3]. Macrophage chemotaxis is severely impaired[3], as is natural killer (NK) cell cytotoxicity[4]. This immune dysfunction may be attributed to malnutrition, altered host cellular metabolism[5] and also to the presence of tumour-derived circulating immunosuppressive factors[3]. Surgical trauma may have a cumulative effect on an already depressed immune system resulting in ideal conditions for tumour growth[1].

Laparoscopy may cause significantly less immunosuppression than conventional laparotomy. This study observed the effect of peritoneal insufflation and laparotomy on host antitumour defence mechanisms in a non-excisional extraperitoneal tumour model.

Materials and methods

Viral and antigen-free C57BL/6 female mice (Charles River, Margate, UK), 8–10 weeks old, were studied ($n = 585$). They were housed in a licensed biomedical facility, allowed to acclimatize for 1 week before the experiments were carried out and fed standard mouse chow and water *ad libitum*. All procedures were carried out under animal licence guidelines of the Ministry of Health, Ireland.

B16 melanoma (NCI Tumour Repository, Frederick, Maryland, USA) syngeneic for C57BL/6 mice was used for these experiments. All experiments were carried out within ten passages of these cells. The cells were prepared for inoculation in calcium- and magnesium-free Hank's Balanced Salt Solution. The B16 melanoma, target-sensitive Yac-1 (for NK cells) and P815 (for lymphokine activated killer (LAK) cells) cell lines (ATCC, Shrewsbury, UK) were used to assess NK and LAK cell cytotoxicity by chromium-51 release assays (CRA).

Study groups

All experiments except the subcutaneous flank injections were carried out using halothane general anaesthesia. Mice ($n = 45$) received a subcutaneous injection of 10^6 B16 tumour cells in the right flank. They were randomized into three groups after flank tumours were induced at 8 days. A control group underwent 20 min of halothane general anaesthesia only. A laparoscopy group had two 18-G and 20-G cannulas (Venflon; Datex-Ohmeda, Dublin, Ireland) placed in four port sites after which a sterile carbon dioxide pneumoperitoneum was established for 20 min (Solos insufflator, St Louis, Missouri, USA) by passing the gas through a 0·2-mm Acrodisc PF filter (Gelman Sciences, Ann Arbor, Michigan, USA) at 4–6 mmHg. A laparotomy group underwent a midline xiphoid to pubis incision exposing the peritoneal contents for 15 min before closure (5 min) with a continous 3/0 nylon suture.

Flank tumours were measured with a Vernier calipers in two dimensions (shortest (a) and longest (b) diameters) every second day for 10 days after operation. Flank tumour volume (V) was calculated using the formula: $V = \pi/6(a^2 + b^2)$[6–8]. This is a reliable and reproducible measure of tumour volume and correlates closely with other parameters for assessing tumour volume such as tumour weight/carcass weight ratios[7]. The change in FTV at each time point was determined by subtracting the FTV of the previous time point from that of the current time point and is referred to as the difference in FTV at each time point. Initial flank tumour experiments were carried out when tumours were

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larger, with the surgical interventions performed at day 14 after tumour inoculation (data not shown); findings were similar to previous experiments performed in this laboratory[9]. The initial pattern of tumour growth in the laparotomy and laparoscopy groups at day 2 was similar to the present findings. However, at day 4 the increase in flank tumour volume was significant in the laparotomy group compared with controls only. This was attributed to the fact that manipulation was performed 2 weeks after injection of the tumour cells when the tumour burden was relatively large and the tumour cells were in a proliferative growth phase, and consequently the trauma of laparotomy would probably have less of an effect on tumour growth than if intervention was performed earlier. For this reason, surgical interventions were performed at 8 days.

Determination of immune function in vitro

C57BL/6 female mice ($n=540$) were randomized into the three groups and the procedures performed as described. They were killed at 24, 48 and 96 h after operation and the spleens were harvested for *in vitro* cytotoxicity assays. Three spleens were pooled for each sample within each group, yielding 20 samples per group at each time point. Ten samples were used for NK and LAK cytotoxicity assays against syngeneic B16 melanoma and the other ten samples for assays against target-sensitive cell lines at each time point. Harvesting of splenocytes, preparation of NK and generation of LAK cells, and 4-h CRA are described elsewhere[4,10] and were modified for use in this study as appropriate. Standard *in vitro* CRA[4,10] were performed using fresh NK and LAK cells against syngeneic B16 melanoma and target-sensitive cells (Yac-1 for NK cells and P815 for LAK cells) at an effector to target ratio of 100 : 1. Spontaneous release was consistently 6 per cent or less of the total incorporated label. Percentage cytotoxicity for each effector cell was calculated as: (experimental counts per minute – spontaneous counts per minute/total incorporated label counts per minute) × 100.

Statistical analysis

Statistical analysis was performed using Statworks and Data Desk application programs on a Macintosh IIvx personal computer (Apple; Cupertino, California, USA; Statworks; Cricket Software, Philadelphia, Pennsylvania, USA; DataDesk 4·1; Data Description, Ithaca, New York, USA). Data are expressed as mean(s.e.m.) and were compared using analysis of variance with least significant difference *post hoc* correction.

Results

Effect of surgery on flank tumour growth

The mean size of the flank tumours at 8 days was 0·50(0·18) cm^3 ($n=45$). The difference in flank tumour volume was significant in both surgery groups compared with the control group at 48 h. The difference in flank tumour growth in the control group was 0·08(0·02) cm^3 compared with 0·25(0·02) cm^3 in the laparoscopy group and 0·34(0·05) cm^3 in the laparotomy group ($P<0{\cdot}01$). This significant increase in growth was maintained in the laparotomy group (0·43(0·05) cm^3) only over the next 48 h compared with both the control (0·18(0·02) cm^3) and laparoscopy (0·20(0·02) cm^3) groups ($P<0{\cdot}01$). The change in FTV at day 2 after laparotomy was significantly greater compared with both laparoscopy and control; this was also true at day 4. There was no further significant increase in flank tumour growth in either group between days 4 and 8 (4 days). Between days 8 and 10 after operation the difference in flank tumour volume in the laparotomy group (0·45(0·04) cm^3) was again significant compared with both the control (0·27(0·03) cm^3) and laparoscopy (0·29(0·04) cm^3) groups ($P<0{\cdot}01$).

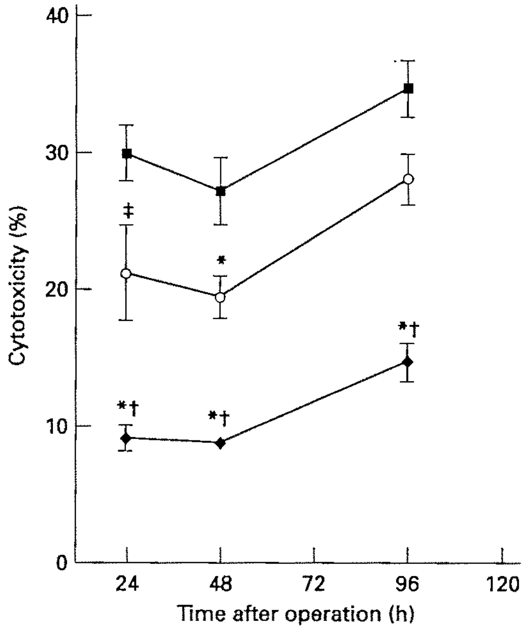

Fig. 1 Natural killer cytotoxicity against Yac-1 after laparotomy (◆), laparoscopy (O) and in controls (■) 24–96 h after operation. *$P<0{\cdot}01$ *versus* control; †$P<0{\cdot}01$ *versus* laparoscopy; ‡$P=0{\cdot}02$ *versus* control; (ANOVA with LSD *post hoc* correction)

Effect of surgery on immune function

NK cell cytotoxicity against the target-sensitive Yac-1 tumour cell line was significantly decreased in the laparotomy and laparoscopy groups compared with controls at 24 h after operation (*Fig. 1*). Furthermore, there was also a significant reduction in cytotoxicity between laparotomy and laparoscopy groups ($P<0{\cdot}01$). This suppression continued to be significant in both groups compared with controls over the next 24 h ($P<0{\cdot}01$) and between the two surgical groups ($P<0{\cdot}01$). By day 4 the suppression remained significant only in the laparotomy group ($P<0{\cdot}01$). The same pattern was observed for NK cell cytotoxicity against syngeneic B16 melanoma. At 24 h percentage cytotoxicities were: control 7·9(1·0), laparoscopy 5·1(0·6) and laparotomy 2·2(0·4) ($P<0{\cdot}01$ and $P=0{\cdot}01$ laparotomy *versus* control and laparoscopy respectively; $P=0{\cdot}01$ laparoscopy *versus* control). Suppression continued at 48 h with control 7·5(0·8) per cent, laparoscopy 5·6(0·4) per cent and laparotomy 2·4(0·3) per cent ($P<0{\cdot}01$ laparotomy *versus* both groups; $P=0{\cdot}01$ laparoscopy *versus* control). At 4 days after operation, NK cell dysfunction persisted significantly in the laparotomy group (5·8(0·3) per cent) only compared with laparoscopy (10·1(0·8) per cent) and controls (12·0(0·8) per cent) ($P<0{\cdot}01$ laparotomy *versus* both groups).

LAK cytotoxicity against the target-sensitive P815 cell line was also significantly reduced in the two operative groups compared with controls up to 48 h after surgery (*Fig. 2*). There was also a significant decrease in cytotoxicity between the laparotomy and laparoscopy groups ($P\leq0{\cdot}01$). This suppression persisted only in the laparotomy group at day 4 ($P<0{\cdot}01$ *versus* control; $P=0{\cdot}02$ *versus* laparoscopy). A similar pattern emerged again in the cytotoxicity against B16 melanoma. Suppression was evident at 24 h in mice that had a laparotomy (7·7(0·4) per cent) and those undergoing laparoscopy (11·2(0·5) per cent) ($P<0{\cdot}01$ both groups *versus* control and laparotomy *versus* laparoscopy). This

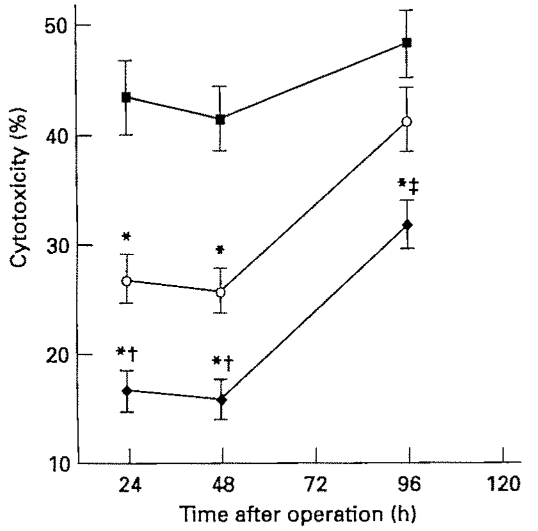

Fig. 2 Lymphokine activated killer cytotoxicity against P815 after laparotomy (◆), laparoscopy (○) and in controls (■) 24–96 h after operation. **P* < 0·01 *versus* control; †*P* = 0·01 *versus* laparoscopy; ‡*P* = 0·02 *versus* laparoscopy; (ANOVA with LSD *post hoc* correction)

persisted at 2 days with percentage cytotoxicities of 19·1(1·6) in controls, 10·2(1·1) in the laparoscopy group and 6·1(1·0) in the laparotomy group (*P* < 0·01 laparotomy and laparoscopy *versus* control; *P* = 0·03 laparotomy *versus* laparoscopy). By 96 h significant suppression occurred only in the laparotomy group (8·6(1·2) per cent) compared with control (26·0(2·5) per cent) and laparoscopy (20·0(2·4) per cent) groups (*P* < 0·01)

Discussion

Since the work by Buinauskas *et al.*[11] and Lewis and colleagues[12], the trauma of major surgery, as well as various forms of anaesthesia[13–18], have been known to induce significant immunosuppression. However, minimal access surgery can now be accomplished with lower morbidity rates and a faster recovery, largely as a result of reduced surgical trauma[19]. There are concerns, however, about the safety of laparoscopic surgery for malignancy[20]. There were fears about port-site recurrences[21–24]. However, results of short-term clinical studies have suggested that laparoscopic resection of colorectal tumours is not associated with an adverse outcome compared with traditional open resection[25–27]. Experimentally, minimally invasive surgery preserves T cell mitogen responses and delayed hypersensitivity[28,29], and tumours develop more rapidly and behave more aggressively after laparotomy than laparoscopy[30]. Redmond *et al.*[31] have shown a preservation of monocyte function in patients undergoing laparoscopic *versus* open cholecystectomy. None of these studies has examined the cellular defects underlying the effects on tumour growth and correlated these with extraperitoneal tumour growth.

The hypothesis was that laparoscopy would preserve immune function and consequently affect tumour growth less than laparotomy in a tumour-bearing host. NK cells were the focus of the studies of immune function as they have been shown to be involved in the recognition and destruction of early developing tumours, activation in response to tumour cell proliferation and limitation of blood and lymph-borne metastatic cells. NK cells are also cytotoxic to many fresh solid tumour cells[32]. LAK cells generated by the stimulation of NK cells by interleukin 2 and interferon γ possess highly potent tumoricidal properties compared with NK cells and NK-resistant tumour cells have been demonstrated to be susceptible to LAK killing *in vitro*[32]. Early work demonstrated the effect of experimental surgical stress on NK cytotoxicity[33–35] and, more recently, NK suppression has been demonstrated after surgery for breast and oesophageal carcinoma[36,37]. Griffith and co-workers[38] have shown a significant decrease in T cell proliferation after open cholecystectomy compared with laparoscopic cholecystectomy but, interestingly, found a small but insignificant decrease in NK cell cytotoxicity in both groups of patients.

Both NK and LAK cell cytotoxicity were significantly suppressed following laparotomy and laparoscopy compared with that in controls up to 48 h after surgery. This early depression of an important antitumour defence mechanism may explain the observed changes in tumour growth. This suppression of immune function persisted significantly in mice that had a laparotomy compared with control animals and with those that had a laparoscopy up to 4 days after operation. This suggests that the acceleration in tumour growth in these animals is due, at least in part, to failure of this first-line defence mechanism.

In the first 48 h, the increase in flank tumour volume was significant in both the laparoscopy and laparotomy groups compared with controls but not between the two surgical groups. This is probably explained by the fact that laparoscopic surgery has been shown to elicit similar responses to laparotomy[28] immediately after operation. The persisting significant NK and LAK dysfunction occurring in mice that had a laparotomy compared with animals in the other two groups between 48 and 96 h after operation provides an explanation for the observed significant and sustained increase in tumour growth.

Several mechanisms have been postulated to be responsible for early postoperative immunosuppression, in particular the production of prostaglandin E_2 by macrophages[39] and the adrenocorticoid stress response[28,31], as well as the emergence of ‘suppressor’ cells that interfere with NK-mediated tumour cell lysis[40]. The size of the surgical wound may be another factor as it is known that the wound is a site of intense immunological activity[41]. However, wound factors could not be responsible for the changes in NK and LAK function and tumour growth in the early postoperative phase as immunosuppressive factors have been found in the wound fluid of rats only 7 days after injury[42]. Although this study only examined the events occurring in the early postoperative period, it could be speculated that the emergence of suppressive factors in the laparotomy wound during the later time points would explain the significant difference in tumour growth 7 days after operation in mice that had a laparotomy.

The immunological changes observed after surgery are complex and multifactorial. This study has shown profound suppression of immune function with correspondingly accelerated tumour growth, even after laparoscopy. The effect after laparoscopy is much less profound and prolonged than after laparotomy, and could have implications for the timing of adjuvant therapy.

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Prospective randomized controlled trial of preservation of the intercostobrachial nerve during axillary node clearance for breast cancer

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Background Complications of axillary surgery occur due to severance of the intercostobrachial nerve (ICBN). The feasibility and benefit of preserving the ICBN to prevent sensory loss was studied prospectively.

Methods Sensory symptoms and deficits were documented, and shoulder movement and arm circumference were measured at discharge and 3 months later in 120 patients randomized to either preservation or division of the ICBN.

Results Preserving the ICBN was feasible in 39 (65 per cent) of the 60 patients randomized to the preservation group. Preserving the nerve prolonged the procedure by a median of 5 min. No difference in sensory symptoms between the groups was seen at 3 months. At 3 months 53 per cent of patients randomized to ICBN preservation had a sensory deficit compared with 84 per cent of those randomized to ICBN sacrifice ($P \leq 0 \cdot 05$).

Conclusion Preserving the ICBN reduces the incidence of sensory deficit (but not symptoms) in patients after axillary clearance.

One of the recognized complications of axillary node clearance is sensory loss or paraesthesia due to division of the intercostobrachial nerve (ICBN)[1,2]. Some surgeons often sacrifice this nerve because of concerns with the thoroughness of clearance, the technical difficulty and their perception of the limited clinical benefit of preserving it. Although the value of preserving the nerve has been claimed[3–6], no randomized study has directly compared nerve preservation with its sacrifice.

Patients and methods

Over 6 months 120 consecutive patients undergoing axillary node clearance for invasive breast cancer were recruited to the study. Patients were randomized to preservation or sacrifice of the ICBN using random numbers. Informed consent was obtained from all patients. Patients were excluded from the study if they had previous axillary surgery, radiotherapy to the axilla, shoulder trauma (or surgery) or were known to have shoulder pathology.

Five surgeons (three consultants and two higher surgical trainees) performed the surgery. As the axillary contents were dissected off the axillary vein and dissection proceeded inferiorly and posteriorly in the medial part of the axilla, the ICBN was routinely encountered running directly across the axillary fat. It was dissected free to the point at which it enters the arm just anterior to where lattisimus dorsi crosses the axillary vein. Caution was taken during the lateral dissection of the axilla where the nerve was in greatest jeopardy; this part of the dissection was performed last. No attempt was made to preserve the lateral branches of the third or fourth intercostal nerves.

Arm circumference and skin thickness were measured at a point 15 cm below the shoulder. Shoulder movements were recorded using a goniometer before and 3 months after surgery. Mapping any sensory deficit to light touch 2·5 cm away from the scar was done at hospital discharge and 3 months after surgery. Light touch sensation was tested in the upper arm at least 2·5 cm away from the axillary or lateral end of a mastectomy incision; sensory deficits in the posterior axillary fold or chest wall were not included. Data concerning drainage volume, seroma and wound complications were also collected. Patients were asked to fill in a questionnaire at review and 3 months after operation.

At 3 months assessment was impossible in four patients because of a language problem (one), senile dementia (one), brain secondaries (one) and severe depression (one).

Statistical analysis

Values are given as median (range). χ^2 test (between groups) and, where appropriate, Fisher's exact test were used to analyse the incidence and changes in sensory symptoms and sensory deficits in the different study groups.

Results

Clinical details

Some 120 women were randomized into the study. Clinical details were similar in both groups. The median age was 58 (range 29–90) years in the group randomized to ICBN preservation and 58 (range 33–88) years in those randomized to ICBN sacrifice. Twenty-two patients (37 per cent) in each group had screen-detected cancers and median inpatient stay was 6 (range 2–14) days in both groups. At 3-month follow-up, 106 patients (88 per cent) attended, 13 refused and one had died 10 weeks after surgery while receiving chemotherapy.

Operative details

Of the 60 patients randomized to ICBN preservation the nerve was actually preserved in only 39 (65 per cent) and was sacrificed in 21 (partially in three patients). In one of the 60 patients randomized to ICBN sacrifice it was pre-

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served by mistake. In total the nerve was actually preserved in 40 patients and sacrificed in 80. In 21 patients in whom preservation was not possible, the nerve was divided accidentally in 18 and deliberately in three in order not to compromise clearance. Surgeons reported technical difficulty in 20 of the 40 patients in whom the nerve was preserved. Preserving the ICBN prolonged the procedure in this group with technical difficulty (clearance and nerve divided, median 35 (range 30–120) min; clearance and nerve preserved, 45 (range 30–90) min). In the remaining 20 patients, although no difficulty was reported in nerve preservation, the procedure was prolonged in 13 by a median of 5 (range 2–5) min.

Axillary lymph node yield was similar in both groups. A median of 14 (range 5–30) nodes were removed in the preserved group and 14·5 (range 6–31) in patients whose ICBN was sacrificed.

Sensory symptoms

The incidence of pain, numbness and diminished or altered sensation in the upper arm was less common in patients randomized to nerve preservation both at discharge and at 3-month review. However, the differences were significant only at discharge and had disappeared by 3 months. Overall 17 (33 per cent) experienced pain in the nerve-preserved group at 3 months and 13 (24 per cent) in the nerve-sacrificed group (*Table 1*).

Sensory deficits

Patients randomized to ICBN preservation had less sensory deficit than those randomized to nerve sacrifice. At discharge, 60 and 78 per cent respectively had a sensory deficit ($P \leq 0{\cdot}05$); 3 months later the respective figures were 53 and 84 per cent ($P \leq 0{\cdot}05$) (*Table 2*). Sensory impairment affected the posteromedial part of the upper arm in most patients; in only two was a deficit present just below the elbow. Comparing the groups in which the ICBN was actually preserved ($n = 40$) or sacrificed ($n = 80$), at discharge 45 and 84 per cent respectively had a sensory deficit ($P < 0{\cdot}001$); 3 months later the respective figures were 61 and 80 per cent ($P = 0{\cdot}06$). Overall, the deficit at discharge was smaller in patients in whom the ICBN was actually preserved than in patients in whom the nerve was sacrificed (median of 49 *versus* 91 cm^2). At 3 months the difference was less obvious (40 *versus* 53 cm^2).

Sensory deficit in the posterior axillary fold and chest wall

This deficit occurred in 44 per cent of patients and was related to injury to the lateral branch of the third and

Table 1 Symptoms at discharge and at 3 months

	Randomized to preserve ($n = 60$)	Randomized to divide ($n = 60$)	*P*	Actually preserved ($n = 40$)	Actually divided ($n = 80$)	*P*
Pain						
At discharge	10 (16)	18 (30)	≤0.05	4 (10)	24 (30)	≤0.05
At 3-month review	8 (16)	13 (24)	n.s.	5 (14)	16 (32)	n.s.
Numbness						
At discharge	15 (25)	32 (54)	0.01	8 (20)	39 (49)	0.004
At 3-month review	25 (49)	37 (67)	n.s.	17 (47)	45 (64)	n.s.
Diminished sensation						
At discharge	23 (38)	36 (60)	0.01	11 (28)	48 (60)	0.002
At 3-month review	33 (65)	41 (75)	n.s.	23 (64)	51 (73)	n.s.
Altered sensation						
At discharge	19 (32)	28 (47)	n.s.	9 (23)	39 (49)	0.01
At 3-month review	22 (43)	25 (46)	n.s.	13 (36)	34 (49)	n.s.

Values in parentheses are percentages. n.s., Not significant, Fisher's exact test

Table 2 Sensory deficits at discharge and at 3 months

	Randomized to preserve ($n = 60$)	Randomized to divide ($n = 60$)	*P*	Actually preserved ($n = 40$)	Actually divided ($n = 80$)	*P*
Normal						
At discharge	24 (40)	13 (22)	≤0.05	22 (55)	13 (16)	<0.001
At 3-month review	19 (47)	9 (16)	≤0.05	14 (39)	14 (20)	0.06
Diminished						
At discharge	20 (33)	30 (50)	≤0.05	9 (23)	41 (51)	≤0.001
At 3-month review	21 (41)	29 (53)	n.s.	14 (39)	36 (51)	n.s.
Loss						
At discharge	5 (8)	8 (13)	n.s.	2 (5)	11 (14)	n.s.
At 3-month review	7 (14)	6 (11)	n.s.	5 (14)	8 (11)	n.s.
Paraesthesia						
At discharge	5 (8)	2 (3)	n.s.	4 (10)	12 (15)	n.s.
At 3-month review	3 (6)	4 (7)	n.s.	3 (8)	4 (6)	n.s.

Values in parentheses are percentages. n.s., Not significant, Fisher's exact test fourth intercostal nerve. The sensory deficit was more frequent in patients who had axillary node clearance in continuity with mastectomy (49 per cent) than in those who had a separate incision (36 per cent). This deficit bore no relation to the sensory loss in the arm.

Questionnaire

Five patients stated that their sensory deficit interfered with normal activities. Twenty-five (49 per cent) of 51 patients who had mastectomy reported feelings of a 'phantom breast' which were painful in seven. Twenty-six women (25 per cent) complained of shoulder stiffness which interfered with daily activities.

Discussion

The management of the axillary nodes in breast cancer is controversial[7-10]. Block dissection of the axillary nodes accurately stages the axilla both qualitatively and quantitatively, and provides a good mechanism for tumour control[7,8]. The majority of surgeons routinely sacrifice the ICBN because of their concern with thoroughness of clearance, technical difficulty involved, and partly because of their underestimation of the clinical benefit of preserving it. Benefits from preserving the ICBN have been identified in several non-randomized studies[2,3,6,11]. Assa[3] reported absence of throbbing and paraesthesia in 12 of 13 patients in whom the nerve was preserved, compared with 'severe' complaints in 33 women with nerve sacrifice. Temple and Ketcham[2] reported 4 per cent sensory loss in 50 patients with a preserved nerve compared with 55 per cent in 15 patients with a sacrificed nerve after 29 months of follow-up.

ICBN preservation is possible in most patients. The high incidence of accidental division in this study may relate partly to a learning curve but a significant number of ICBNs cannot be preserved because they divide into small branches.

The incidence of sensory symptoms in patients whose nerves were actually preserved was higher than that reported in other studies. Moreover, by 3 months symptoms had worsened in both groups, particularly in patients whose nerve was preserved. Unlike previous reports[2,3,6] in which nearly all patients with a sacrificed nerve developed symptoms, in this study two patients with objective sensory loss had no sensory symptoms while eight patients with sensory symptoms had no objective sensory deficit. The incidence of sensory deficits in the group randomized to nerve preservation was reduced both at discharge and at 3 months indicating the value of preserving the nerve where possible.

Sacrificing the ICBN did not affect shoulder movement or the amount of axillary drainage and seroma formation. While at least one study reported that preserving the ICBN did not increase the rate of local recurrence[3], the theoretical risk of compromising the thoroughness of axillary node clearance has not been assessed. The lymph node yield was similar between the groups indicating that preserving the nerve did not compromise the extent of clearance.

All patients received a full explanation, warning and reassurance about potential sensory loss before surgery but, despite this, symptoms were a cause for concern in the majority of patients.

The morbidity resulting from division of the ICBN during axillary surgery is significant. Attempting nerve preservation prolongs the operation and is not possible in every patient. It is sensible practice to attempt to preserve the ICBN whenever possible.

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Diagnosis and conservative management of intrathoracic leakage after oesophagectomy

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Background Although intrathoracic leakage is a major complication of oesophagectomy, precise data concerning diagnostic features and results of conservative treatment are lacking.

Methods From 1986 to 1994, 409 oesophagectomies with stapled oesophagogastrostomy were performed, including 358 Lewis–Tanner and 51 Sweet procedures. A water-soluble contrast swallow was routinely performed on day 7 or later, before oral intake was begun. All patients except one received conservative non-surgical treatment, including nutritional support and perianastomotic drainage.

Results Leaks were diagnosed in 38 patients (9·3 per cent). The leakage rate was 7·8 per cent after the Lewis–Tanner procedure and 20 per cent after the Sweet procedure ($P < 0·01$). Eleven patients had no symptoms. Seven of the 27 patients with symptoms had a contrast swallow that was normal, and subsequently developed a confirmed fistula after the onset of oral intake. Five patients had to undergo reoperation. All asymptomatic patients and 18 symptomatic patients recovered. Nine patients died, mainly from multiple organ failure, including three who had reoperation for resection of the gastroplasty.

Conclusion The potential presence of clinically silent fistula and the deleterious role of oral intake still justify routine detection of leakage after oesophageal resection. Conservative treatment results in survival with preservation of the gastroplasty in most patients, unless multiple organ failure occurs.

Intrathoracic leakage is the most serious surgical complication of oesophagogastric resection and is responsible for approximately 40 per cent of postoperative deaths[1–3]. As a result of the significant mortality rate due to leakage, ranging from 12 to 36 per cent, many authors have attempted to define the predictive factors for this complication[1,2,4], but the results are unclear, and the best way to perform an oesophagogastric anastomosis remains to be established[1]. In most centres, routine detection of leakage with a water-soluble contrast swallow is performed before onset of oral intake but both the clinical value and the safety of this examination have been criticized[5]. There is no uniform method for managing patients with intrathoracic leakage; some authors recommend early reoperation[6] while a conservative approach is used in most cases by other groups[7] including ours. This retrospective study reports on the diagnostic features and results of a conservative approach for the treatment of intrathoracic leakage complicating oesophageal resection for carcinoma.

Patients and methods

From 1986 to 1994, 409 consecutive patients underwent oesophagogastrectomy for oesophageal ($n = 327$) or cardial ($n = 82$) carcinoma. There were 358 Lewis–Tanner procedures, including laparotomy for gastric mobilization and right thoracotomy for subtotal oesophagectomy, and 51 Sweet procedures, including left thoracotomy with phrenotomy for gastric mobilization and oesophagectomy below the aortic arch. The operations were performed by 16 different surgeons, including four experienced surgeons who had performed at least 50 procedures.

In all cases, a gastric tube was created by application of a GIA (AutoSuture, Flaucourt, France) or PLC (Ethicon, Neuilly, France) stapler close to the lesser curvature. The oesophagogastric anastomosis was completed with an ILS (Ethicon) or EEA (AutoSuture) stapler at least 3 cm from the gastric closure line. The largest stapler that could fit in the oesophagus was used. When the doughnuts were incomplete, the anastomosis was reconstructed or extra sutures were added depending on the size of the defect. A perianastomotic omental wrap was used routinely[7]. Gastric drainage was improved by pyloroplasty during the Lewis–Tanner procedure and by pyloric dilatation during the Sweet procedure.

A nasogastric suction tube was maintained until the seventh postoperative day. A meglumine diatrizoate swallow was performed on day 7 or later, depending on the patient's condition. Oral intake was commenced when the anastomosis appeared regular with a uniform diameter. Certain critically ill patients who could not eat received an injection of either methylene blue through the nasogastric tube when chest drainage was still in place or meglumine diatrizoate during computed tomography (CT). Anastomotic leakage was diagnosed by (a) extravasation of contrast medium, (b) leakage of methylene blue through the drains, or (c) the presence of at least two species of endogenous bacteria in the chest drainage fluid. Closure of the fistula was assessed by repeat contrast swallow.

Symptoms related to anastomotic fistula were classified as follows: (a) sepsis (temperature greater than 38·5°C); (b) respiratory failure (need for postoperative ventilatory support for more than 2 days); and (c) multiple organ failure (MOF). All patients except one received non-surgical treatment, including nutritional support and perianastomotic drainage. Symptomatic patients were treated in an intensive care unit when ventilatory or haemodynamic support was necessary.

Statistical analysis

Statistical significance was determined with the χ^2 test with Yates' correction when indicated. $P < 0·05$ was considered statistically significant.

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Results

Diagnosis

Intrathoracic anastomotic leakage was diagnosed in 38 patients (9·3 per cent) of mean(s.d.) age 59(11) (range 36–83) years. Leaks occurred from 2 to 28 (median 12) days after surgery and before the seventh post-operative day in eight patients. The rate of leakage was 7·8 per cent after the Lewis–Tanner procedure and 20 per cent after the Sweet procedure ($P < 0{\cdot}01$) (*Table 1*).

Diagnostic features in the 38 patients with leaks are shown in *Table 2*. In the 11 asymptomatic patients, leakage was diagnosed by contrast swallow on day 7 and was subsequently confirmed by the disappearance of extravasation of the contrast medium in a further examination performed at least 10 days later. In the 27 patients with a radiologically proven fistula, 22 had limited perianastomotic extravasation of the contrast medium and five had massive opacification of a pleural cavity or the mediastinum. Seven patients had a normal contrast swallow on day 7 and developed symptoms after the onset of oral intake; a fistula was subsequently diagnosed following a further contrast examination or a methylene blue test.

Aetiological factors

Problems with the anastomosis procedure were noted in 14 patients who developed leakage. Venous stasis was present in the upper part of the stomach in six patients while technical difficulties requiring a second attempt at anastomosis occurred in six others. Two other patients had a markedly thickened stomach wall. Other factors that may have resulted in a predisposition to fistula were perioperative hypotension[8] (systolic blood pressure less than 90 mmHg for more than 6 h) in 12 patients, cirrhosis with portal hypertension[9], preoperative chemoradiotherapy[10] and postoperative distension of the gastric transplant[8,10] diagnosed on chest radiography in three patients each. No predisposing factors could be found retrospectively in six patients.

The location of the fistula was determined radiologically or during reoperation in 27 patients: 19 were located at the oesophagogastric anastomosis, three were a result of leakage of the upper gastric closure, and five were complex with both anastomotic and upper gastric leakage.

The leakage rate per surgeon was 7·1 per cent (17 of 241) for the four most experienced surgeons and 12·5 per cent (21 of 168) for the 12 others (P not significant).

Table 1 Leakage complicating Lewis–Tanner and Sweet procedures

	Lewis–Tanner ($n = 358$)	Sweet ($n = 51$)
No. of leaks	28 (7·8)	10 (20)*
Asymptomatic	6 (1·7)	5 (10)*
Symptomatic	22 (6·1)	5 (10)
Treatment of leaks		
Enteral nutrition	6	3
Total parenteral nutrition	22	7
Reoperation	3	2
Deaths		
Due to leakage	6 (1·7)	3 (6)
Overall	23 (6·4)	5 (10)

Values in parentheses are percentages. *$P < 0{\cdot}01$ (Sweet *versus* Lewis–Tanner procedure, χ^2 test)

Table 2 Diagnostic features in patients with leaks complicating oesophagectomy

	Patients with leaks ($n = 38$)
Symptoms	
Absent	11
Present	27
Sepsis	10
Respiratory failure	9
Multiple organ failure	8
Method of diagnosis	
Radiology	27
Methylene blue test	7
Bacteriology of chest drainage fluid	4

Treatment

Initial conservative non-surgical treatment was administered to all patients except one who had a fistula confirmed by methylene blue test at day 2 and immediately underwent reoperation to reconstruct the anastomosis. Twenty-nine patients received total parenteral nutrition, including six with asymptomatic fistula (*Table 1*). Nine patients received enteral nutrition through a fine weighted feeding tube placed endoscopically in the distal duodenum, including five who were asymptomatic. Perianastomotic drainage was performed in all cases, using the *in situ* pleural drains in 13 patients and a percutaneous CT-guided drain in 24.

Five patients underwent reoperation, including the patient who had reoperation on day 2. One patient underwent reoperation on day 23 because of ineffective percutaneous pleural drainage. Three patients had reoperation on days 14, 18 and 71 due to persistent symptoms despite intensive care support; these three patients had resection of a necrotic gastric transplant with cervical oesophagostomy and feeding jejunostomy.

Reoperation was performed in one of the eight patients with leakage diagnosed before day 7 and in four of the 30 in whom leakage was diagnosed on day 7 or later (P not significant).

Follow-up

In all 11 asymptomatic patients, leakage resolved within 16–59 (median 33) days with medical treatment. Nine of the 27 symptomatic patients died, resulting in a 24 per cent overall mortality rate. Three of five reoperated patients and all eight patients with MOF died. Two of the three patients who underwent resection of the gastric transplant died from persistent MOF and one died from respiratory failure. Of the seven patients who developed leaks after a normal contrast swallow, two died. The mortality rate due to leakage after Lewis–Tanner and Sweet procedures was 1·7 per cent and 6 per cent respectively (P not significant). Median hospital stay before discharge was 44 (range 21–102) days in the 18 surviving symptomatic patients and 42 (range 11–120) days in those who died.

With follow-up ranging from 16 to 122 months, no benign anastomotic stenosis was observed in asymptomatic patients while two of the 18 surviving symptomatic patients later developed a benign anastomotic stricture which was successfully treated by endoscopic dilatation.

Discussion

In the present study, the rate of leakage after the Lewis–Tanner procedure was 7·8 per cent, resulting in a 1·7 per cent mortality rate due to leakage. These results are consistent with recent studies[1–4] and indicate that the Lewis–Tanner procedure is safe. On the other hand, a significantly higher rate of leakage (20 per cent) was observed after the Sweet procedure. There is no clear explanation for this finding, although Peracchia *et al.*[4] have reported a significantly higher rate of leakage for oesophageal anastomoses located between the azygos vein arch and the lower pulmonary vein, which suggests that the oesophageal wall is of poorer quality at this level. The high prevalence of leakage and other drawbacks, including postoperative reflux and gastric outlet syndrome[11], make the use of the Sweet procedure debatable.

There is often a predisposing factor in patients with leakage complicating oesophagectomy, as observed in 32 of the 38 patients in this study. This seems to indicate that most leakages are avoidable. The importance of the venous drainage of the gastric tube is emphasized by the occurrence of leakage in patients with peroperative congestion over the gastroplasty, as well as by the fact that eight patients developed necrosis of the gastric wall or leakage of the gastric closure far from the anastomotic site. Diagnosis and treatment of leakage did not differ in these patients.

The role of the technique used to construct the oesophagogastrostomy is less clear. Several retrospective studies have suggested that mechanical anastomoses are less likely to result in leakage than manual ones[2,4,7]. More recently, a multi-institutional controlled trial reported similar early results for manual and mechanical oesophagogastric anastomoses[1]. Although an omental graft surrounding the anastomosis was used routinely, the influence of this measure on the rate of fistula formation cannot be concluded from this study. However, omental wraps may well prevent the occurrence of oesophago-aortic fistulas since none of the present patients developed this complication.

In the authors' experience, water-soluble contrast swallow on the seventh postoperative day did not detect leaks accurately. This point has rarely been reported in the literature[12,13]. One reason could be underestimation of limited leaks by water-soluble contrast medium, and the later increase in these leaks following oral intake. For this reason some authors advocate the use of barium to enhance the sensitivity of contrast swallow[14]. Another explanation could be a too early detection of fistula before anastomotic healing. This hypothesis is not supported by the literature since most groups perform contrast swallow between days 3 and 8 after operation[1,3,4]. Only one group performs this examination on the tenth postoperative day[2]. Some leakages undetected on contrast swallow can be diagnosed by CT, suggesting greater accuracy in the latter[15]. Patients with clinically asymptomatic leaks (11 of 38 in the present study) were separated from those with symptomatic leaks, as a previous study reported a 41 per cent rate of leaks detected radiologically[1]. This contrasts with the results of Wong *et al.*[5], who did not observe any leaks without clinical evidence and who discontinued the routine use of contrast swallow.

The present study showed that a conservative approach allows survival with preservation of the gastric transplant in two-thirds of symptomatic patients. A conservative approach is used widely to treat minor or symptom-free leaks[8,10,12]. In this situation, nutritional support is usually provided through parenteral access[2] or a jejunostomy tube[3,16]. The present study used enteral nutrition through a fine weighted feeding tube which was placed in the duodenum once the leak had been diagnosed. No complications occurred with this technique in any of the nine patients who received this type of support. This approach is interesting as it does not have the disadvantages of parenteral nutrition or routine jejunostomy[16].

In patients with severe symptoms, including respiratory distress and MOF, the use of a conservative approach is still being debated. Some authors suggest reoperation[2] whereas a conservative approach is used in most cases by other groups[3]. Reoperation is clearly indicated for leaks from technical failure without gastric wall necrosis[17], as observed in one of the present patients who underwent successful reoperation on day 2. Otherwise, leaks are usually due to gastric necrosis, and early reoperation is performed to improve drainage[18] or to take down the anastomosis[10]. Anastomosis take-down with gastrostomy and cervical oesophagostomy is a complex operation resulting in a hazardous delayed reconstruction[10]. For this reason, the authors recommend a conservative approach as long as the consequences of leakage are limited. Indeed all the patients who presented with pulmonary distress survived without reoperation, except one. On the other hand, all the patients who developed MOF died, including three who had reoperation. In the present study, as in others, excessive delay seems to be the most likely explanation for the high mortality rate following reoperation, which ranges from 33 to 100 per cent[1,2,10,18]. These results suggest that reoperation for leaks should be performed as soon as MOF is diagnosed.

In conclusion, the potential presence of a clinically silent fistula and the deleterious role of oral intake still justify routine detection of leakage after oesophagogastric resection. However, a normal contrast swallow does not prevent the later occurrence of a potentially fatal leak. Conservative treatment allows survival with preservation of the gastroplasty in symptomatic patients unless MOF occurs. Prompt reoperation is probably the best chance of survival in patients with leakage complicated by MOF.

Acknowledgements

J. Baltar was supported by a grant from the Spanish Funds for Health Survey (FIS no. 94/5355).

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Corrigendum

D. A. McNamara, J. H. Harmey, T. N. Walsh, H. P. Redmond and D. J. Bouchier-Hayes. Significance of angiogenesis in cancer therapy. *Br J Surg* 1998; 85: 1044–1055.

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British Journal of Surgery 1998, 85, 1450–1452

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Abdominal ultrasonography in the diagnosis of colonic cancer

Sir

We read with interest the article by Richardson *et al.* (*Br J Surg* 1998; 85: 530–3). The method is non-invasive and avoids bowel preparation and exposure to radiation, but it may be suboptimal. Overlapping gas-filled small and large bowel loops may obscure a mass. Other colonic pathology, such as diverticular disease, non-specific colonic wall thickening and small polyps, may decrease the overall diagnostic ability of ultrasonography.

The authors did not address the possible pitfalls and disadvantages. The colon is tortuous and studying the whole length may be time-consuming, especially in obese patients. Ultrasonography is operator-dependent and the operator should be adequately trained in abdominal scanning.

The value of ultrasonography in localizing colonic tumours has been proven[1], but surgeons also appreciate the demonstration of associated polyps, fistulous communications and confirmation of the site by barium enema or colonoscopy. This results in optimum preoperative planning and counselling of the patient before surgery.

While ultrasonographic detection of a colonic mass may be accurate when barium enema or colonoscopy is not possible, we believe it should not become the first investigation of choice. However, ultrasonography may well become the screening method of choice for colonic neoplasms, perhaps with better compliance rates than conventional screening methods.

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1 Lim JH, Ko YT, Lee DH *et al.* Determining the site and causes of colonic obstruction with sonography. *AJR Am J Roentgenol* 1994; 163: 1113–17.

Authors' reply

Sir

We are grateful for the interest shown by Harinath and Jones in our paper. We found that the addition of colonic images to routine abdominal ultrasonography resulted in only a slight increase in duration of the examination. We agree that obesity and, to a lesser extent, bowel gas, does affect the sensitivity and that non-malignant colonic pathology could affect the specificity of ultrasonography in the diagnosis of colonic malignancy, although colonic tumours often have a diagnostic appearance. In our study, the sensitivity and accuracy of the technique was over 90 per cent in both cases and abdominal ultrasonography detected four cases of colonic carcinoma that had been missed by barium enema because of diverticular disease. The technique is inevitably operator-dependent, but colonic images are usually ignored and we feel that interpretation of these images is only a short extension of routine abdominal ultrasonography interpretation and could easily be learnt with practice.

Assessment of the whole colon is important and we are not advocating abdominal ultrasonography as a replacement for colonoscopy and barium enema, which remain the primary investigations for colonic pathology. There are, however, patients in whom neither of the latter is possible due to technical problems. In such patients abdominal ultrasonography might provide valuable diagnostic information and we encourage the addition of examination of the large bowel to routine abdominal ultrasonography; surgeons should request this from radiological colleagues.

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Multidisciplinary approach to biliary complications of laparoscopic cholecystectomy

Sir

The review of biliary complications of laparoscopic cholecystectomy in a single institution (*Br J Surg* 1998; 85: 627–32) has, as its corollary, the retrospective review of the late development of visceral abscesses related to gallstone 'spillage'[1]. As with bile duct injury, this occurs more commonly after laparoscopic than open cholecystectomy[1]. Horton and Florence[1] reviewed 1130 laparoscopic cholecystectomies and found four patients who developed late abscesses following gallstone spillage. This might have been an underestimate, since stone spillage was not always recorded in the operative notes and patients readmitted to other hospitals may have been overlooked. Bile duct injury and spillage-related abscess comprise the two most 'distinctive' complications of the laparoscopic approach[1], justifying documentation more rigorous than that afforded by the inherently flawed retrospective methodology. The minimum requirement should be a prospective study documenting in the same cohort bile duct injury, gallstone spillage and any sequelae. The relative prevalence of these complications and the level of experience and degree of supervision of the surgeons involved would be documented. Follow-up procedures would need to be defined prospectively.

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Author's reply

Sir

Dr Jolobe highlights an important but rare complication of cholecystectomy, namely the development of an abscess related to gallbladder stone spillage at the time of laparoscopic cholecystectomy. I would agree that this complication is often not well documented at the time of surgery and both bile duct injury and gallbladder stone spillage have increased in the era of laparoscopic cholecystectomy. Prospective audits have suggested the incidence of biliary injury to be declining towards those of the prelaparoscopic era[1,2]. This is likely to represent a technical improvement with experience and will hopefully be reflected by a reduced incidence of late intra-abdominal abscess related to stone spillage. Continued careful audit of laparoscopic cholecystectomy is, however, required to highlight this important late complication.

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Prospective randomized controlled trial to compare skin staples and polypropylene for securing the mesh in inguinal hernia repair

Sir
We read with interest the recent article by Mills *et al.* (*Br J Surg* 1998; 85: 790–2) comparing prospectively the use of skin staples and polypropylene for securing mesh in inguinal hernia repair. This was a well conducted study and manages to correct the shortcomings pointed out[1] in a previous paper on the same topic[2].

We work in a busy district general hospital and using theatre time efficiently is extremely important but not at the cost of the quality of service provided. In recent months we have also used the skin staple technique to secure mesh in inguinal hernia repair and our experience has shown it to be a much quicker technique. We were able to decrease operating time for the Lichtenstein repair using staples by at least 10 min. The repair proved equally as effective as that with polypropylene suture and has not shown any greater complications in the short term.

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Randomized placebo-controlled trial of local anaesthetic infusion in day-case inguinal hernia repair

Sir
We read the article by Oakley *et al.* (*Br J Surg* 1998; 85: 797–9) with interest. It would appear that they have been able to achieve significant improvements in postoperative pain in patients undergoing an open Lichtenstein repair. There are many who claim that day-case open hernia repair under local anaesthetic is associated with a relatively painless recovery. This study seems to suggest that there is considerable room for improvement. We have long been of the opinion that the open hernia repair is associated with considerable postoperative pain and this unit has evaluated 121 patients who have had a previous open repair and a subsequent laparoscopic hernia repair for recurrence of or new contralateral hernia. On a comparative pain score 97 per cent of these patients recorded the laparoscopic repair as being associated with significantly less pain. The laparoscopic extraperitoneal repair is now the repair of choice and we have performed over 500 with all patients completing a visual analogue score questionnaire as in Oakley *et al.* Although better pain control appears to be achieved with the local anaesthetic infusion for the first 24 h, beyond this time the laparoscopic repair achieves comparable pain scores to local anaesthetic infusion. The use of local anaesthetic infusion appears to be a good compromise when open repairs are performed but the best solution may well be to offer the patient a procedure which is inherently less painful.

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Functional results following the antegrade continence enema procedure

Sir
The paper by Shankar *et al.* (*Br J Surg* 1998; 85: 980–2) provides further evidence that the Malone antegrade continence enema (ACE) procedure has been a major advance in the management of faecal incontinence in selected patients. Between 70 and 80 per cent of reported patients have achieved faecal continence between colonic washouts but the appendicostomy, which provides access to the caecum, remains a major source of morbidity. Surgical complications are common (*Table 1*).

Preliminary experience with nine patients (two with a high anorectal malformation and seven with spinal dysraphism, two of whom are wheelchair-bound) with a median age of 8 years and followed for a median of 9 months, indicates that insertion of a caecostomy button rather than construction of a catheterizable appendicostomy avoids most of these complications. Our practice

Table 1

Author	Year	*n*	A	C	Median age (years)	Surgical complications Relaparotomy	Stomal stenosis	Leakage	Wound infection
Griffiths and Malone[1]	1995	21	20	1	12	3	6	0	1
Wilcox and Kiely[2]	1998	36	30	6	8	1	12	2	1
Shankar *et al.*[3]	1998	40	33	7	11	2	18	2	5

A, Appendicostomy; C, tubularized caecal flap has been to insert a catheter into the caecum via a Lanz incision and change the tube caecostomy to a button 6 weeks later. Others have recently reported the direct operative insertion of a caecal button[4]. We have experienced no surgical complications to date and all patients are successfully performing colonic washout through the button every 24–48 h. The technique has other benefits: if necessary, the appendix can be preserved for urological reconstructive surgery and should the ACE be unsuccessful, reversal is theoretically simple. The potential disadvantages of the button technique relate to distortion of body image, the need to treat granulations around the track and the need to replace the button when mechanical failure occurs. Percutaneous insertion of newer, less obtrusive, devices is being explored in some centres[5].

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Temporary decompression after colorectal surgery: randomized comparison of loop ileostomy and loop colostomy

Sir

We were interested in the paper by Gooszen *et al.* (*Br J Surg* 1998; **85**: 76–9) as we have recently reviewed our own experience of loop ileostomy closure. We agree that loop ileostomy is not without complications and we also restrict its use to specific indications, primarily low anterior resection with total mesorectal excision. However, we feel that the conclusion that transverse colostomy is preferable to loop ileostomy is not fully supported by the data.

The difference in the complication rate between the two groups after stoma construction only becomes significant when general complications, rather than just stoma-related complications, are included. The higher rate of general complications in the loop ileostomy group could well be influenced by the heterogeneous indications for construction of the stoma, especially as the 'compromised anastomoses' were almost twice as frequent in the loop ileostomy group. Patients with a loop ileostomy had significantly fewer complications during the interval between operations than those with a loop colostomy, except in the need to modify their diet. In the period immediately after stoma closure, there was no significant difference in the complication rate between the loop ileostomy and loop colostomy groups. They report one anastomotic leak after loop ileostomy closure (causing death). We have had two leaks in patients undergoing 36 loop ileostomy closures, but no deaths. Interestingly, histology of the dehisced small bowel anatomosis in one patient whose stoma closure leaked showed evidence of radiation damage. With the increasing use of preoperative radiotherapy for patients with rectal cancer, it may be prudent to avoid fashioning a stoma from a loop of ileum tethered deep in the pelvis.

We do not feel there is hard evidence in favour of loop colostomy over loop ileostomy. Colostomy prolapse is common and distressing for the patient. The study by Gooszen *et al.* reports a 42 per cent incidence of prolapse with loop colostomy, whereas only one of the 32 ileostomies prolapsed during the follow-up period. In our series of 36 patients there was only one prolapse. Unless hard evidence appears in support of routine use of loop colostomy we will continue to use loop ileostomy.

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Author's reply

Sir

The letter from Torkington *et al.* illustrates the impact of personal preference in the use of ileostomy or colostomy. We began the study to support our own impression that loop ileostomy was superior to loop transverse colostomy. We did not conclude. that 'transverse colostomy is preferable to loop ileostomy' but that, based on the data collected, 'loop ileostomy is not the stoma of preference'. This means that we believe there are reasons (proposed by Torkington *et al.*) to prefer ileostomy, but that there are complications (even leading to death) occurring at least as frequently as after colostomy. We are glad that two leaks after ileostomy closure did not cause death in the series by Torkington *et al.*, but we cannot exclude the complications we registered. Although their comment about statistical significance is justified, we can neither ignore the general complications nor disregard them as unrelated to the type of stoma. By covering the full-time period from first operation until stoma closure all relevant issues from the patient's and doctor's perspectives were observed and we cannot come to any other conclusion. Their experience with loop ileostomy is apparently satisfactory and that indicates that, with dedication to this technique, it is possible to attain good results, but this cannot lead us to a different conclusion from that achieved in our multicentre study.

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British Journal of Surgery 1998, 85, 1453

Book reviews

Wounds in Biology and Management

D. J. Leaper and K. G. Harding (eds). 282 × 222 mm. Pp. 198. Illustrated. 1998. Oxford: Oxford University Press. Price not supplied.

Books on wound healing are relatively uncommon; this one manages to be practical as well as a detailed reference book on all aspects of wound healing. It covers all the new aspects of the subject, including advances in growth factor research and theories underlying wound dressings. It will appeal to many groups and is a 'must' for all medical libraries. It is comprehensive for the surgical trainee who may be expected to know the basic steps in wound healing and factors influencing it, and will appeal to many senior surgeons with an interest in tissue repair mechanisms. It has excellent chapters on the phases of wound repair, factors influencing wound healing, the management of traumatic wounds and the role of infection. This is the most comprehensive and up-to-date book on the subject currently available and the authors have succeeded in covering every aspect of wound healing while still producing a readable volume. It lacks a little on continuity of style, due to multiple authorship of its chapters. The illustrations let it down somewhat and there seemed little point in the colour plates being mere copies of earlier black and white photographs. I had the slight feeling throughout the book that the illustrations were what came to hand rather than being pertinent to the text. More diagrams to break up the text would have been more reader-friendly. Overall, however, this is an excellent book; it is *the* current general reference book on wound healing.

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A Primer on Amputations and Artificial Limbs

G. Murdoch and A. B. Wilson Jr. 260 × 184 mm. Pp. 295. Illustrated. 1998. Springfield, Illinois: Charles C Thomas Publisher. $63.95.

Amputation surgery is often delegated to trainees who may not appreciate the impact of surgical technique upon rehabilitation. Thus, this text appeared to have considerable promise. While descriptions of operative techniques are good, the sections on preoperative and postoperative management for different amputations are repetitive, and discussion of the merits of different amputations often reflects author prejudice. In particular, the case for below-knee rather than above-knee amputation is made on the basis of a lower mortality rate, ignoring the comorbidity present in patients requiring the former procedure. In critical ischaemia it is often difficult to decide whether a below-knee amputation will heal and studies on level selection are reviewed. The reader is advised that a Doppler pressure just above the knee of over 50 mmHg, 50–70 mmHg or over 70 mmHg is the most reliable indicator of healing, depending on which chapter is being read. The text concludes with a review of prostheses; I suspect there is too much information here to interest surgical trainees but not enough for those working in a rehabilitation unit. In summary, this book is unlikely to have wide appeal as much of the information relevant to surgical trainees is available in standard vascular and orthopaedic textbooks.

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Atlas of Endoscopic Perforator Vein Surgery

P. Gloviczki and J. J. Bergan (eds). 285 × 220 mm. Pp. 265. Illustrated. 1998. Heidelberg: Springer. £192.

It would be surprising if the internationally known and highly respected editors of this work were to offer anything other than a sophisticated, visually attractive, readable and up-to-date book; I was not surprised. For those considering embarking on subfascial endoscopic perforator vein surgery (SEPS), this work sets out the present position of the art in its chronological setting in a polished fashion that is not available elsewhere. Chapters are offered on the technical equipment required, the gas insufflation method, the open technique, creation of a subfascial space, subfascial dissection and perforator ablation, and comparison of SEPS with the open Linton operation. The volume ends with a section on the results of the North American Subfascial Endoscopic Perforator Surgery Registry. The book is illustrated liberally with 236 beautifully presented figures, many of them in colour. I suppose this is the reason for medical authors once again usurping the term 'atlas' in the title; I myself would have preferred a more straightforward approach, *Endoscopic Perforator Vein Surgery Illustrated* (or something similar).

However, the prospective buyer should beware. Less than one-third of the book's 265 pages (the chapters outlined above) are directly concerned with SEPS. The rest deals with epidemiology, pathology, classification of and tests for venous disease, standard open surgery, medical and compression treatment of venous ulcers, and deep vein thrombosis prophylaxis. Further space is given to 'profiles' of no fewer than 19 distinguished vascular surgeons of past years; these are dispersed between chapters. All of this gives the impression that there is just not enough material on SEPS itself to fill a respectably-sized book; but even the padding is quality stuff.

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Scientific Surgery

The British Journal of Surgery is committed to practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English language publications. The full list of all these papers will be available in the Scientific Surgery Archive which will be held on *The British Journal of Surgery* website together with links to free Medline sites where abstracts can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Randomized trials

Berridge DC, Starky G, Jones NA, Chamberlain J. A randomized controlled trial of double *versus* single-gloving in vascular surgery.
J R Coll Surg Edinb 1998; 43: 9–10.
Eighty-nine consecutive vascular procedures were studied; double-gloving reduced the rate of hand contamination for surgeons but appeared to increase the number of glove perforations

Prior MJ, Williams EV, Shukla HS, Phillips S, Vig S, Lewis M. Prospective randomized controlled trial comparing Lichtenstein with modified Bassini repair of inguinal hernia.
J R Coll Surg Edinb 1998; 43: 82–6.
In this study of 80 patients, postoperative pain scores were significantly lower after Lichtenstein repair, although analgesic requirements were similar. Complication rates and convalescence times were similar.

Lo C-M, Liu C-L, Fan S-T, Lai ECS, Wong J. Prospective randomized study of early *versus* delayed laparoscopic cholecystectomy for acute cholecystitis.
Ann Surg 1998; 227: 461–7.
In this trial including 99 patients, initial conservative treatment followed by interval cholecystectomy did not reduce the morbidity rate (29 *versus* 13 per cent for acute operation) but did prolong overall hospital stay and the recuperation interval

Lau JYW, Lo S-Y, Ng EKW, Lee DWH, Lam Y-H, Chung SC. A randomized comparison of acute phase response and endotoxemia in patients with perforated peptic ulcers receiving laparoscopic or open patch repair.
Am J Surg 1998; 175: 325–7.
Twenty-two patients were randomized. Three of 11 assigned to laparoscopy required open patch repair. There was no difference in the biochemical markers of the acute stress response when laparoscopic and open repair were compared.

Zieren J, Zieren HU, Jacobi CA, Wenger FA, Muller JM. Prospective randomized study comparing laparoscopic and open tension free hernia repair with Shouldice's operation.
Am J Surg 1998; 175: 330–3.
Randomization included 240 patients. Laparoscopic repair took longer and was more expensive. Complication rates in each group were similar and there were no recurrent hernias. Postoperative pain and time to return to work were similar for laparoscopic and tension-free repairs; Shouldice repair was more painful and convalescence was longer.

European Carotid Surgery Trialists Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST).
Lancet 1998; 351: 1379–87.
This multicentre study included 3024 patients followed for a mean of 6·1 years For carotid stenoses greater than 80 per cent the 3-year stroke and death rate was reduced from 26·5 to 14·9 per cent by carotid endarterectomy. The individual benefit was reduced by increasing patient age and female sex

Cao P, Giordano G, De Rango P, Zanetti S, Chiesa R, Coppi G *et al.* A randomized study on eversion *versus* standard carotid endarterectomy: study design and preliminary results – the EVEREST Trial.
J Vasc Surg 1998; 27: 595–605.
This multicentre trial involved 1353 patients. Perioperative stroke and death rates were similar (1 3 per cent in both groups). Longer follow-up is needed to determine any differences in the rate of restenosis

The European TAO Study Group. Oral Iloprost in the treatment of thromboangiitis obliterans (Buerger's disease): a double-blind, randomised, placebo controlled trial.
Eur J Vasc Endovasc Surg 1998; 15: 300–7.
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Bonnema J, van Wersch AMEA, van Geel AN, Pruyn JFA, Schmitz PIM, Paul MA *et al.* Medical and psychosocial effects of early discharge after surgery for breast cancer: a randomised trial.
BMJ 1998; 316: 1267–71.
One hundred and thirty-nine women with operable breast cancer were enrolled; 69 were randomized to discharge home 4 days after surgery with drains *in situ*. The rest were discharged after the drains were removed (mean 9 days). There were no differences in wound complication rates or degree of satisfaction based on detailed psychological measurements.

Scriven JM, Taylor LE, Wood AJ, Bell PRF, Naylor AR, London NJM. A prospective randomised trial of four-layer *versus* short-stretch compression bandages for the treatment of venous leg ulcers.
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Sixty-four ulcerated legs were randomized. Healing rates at 1 year were similar (55 *versus* 57 per cent) but there were four significant complications after short-stretch compression bandaging

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British Journal of Surgery 1998, 85, 1457–1459

Leading article

Classification of adenocarcinoma of the oesophagogastric junction

In the Western world there has been an alarming rise in the incidence and prevalence of adenocarcinoma at the oesophagogastric junction. However, much discrepancy exists in the current literature about the classification and optimal management of this tumour. While some consider and treat all tumours arising in the vicinity of the oesophagogastric junction as oesophageal cancer, others regard them as gastric cancer, or even as an entity separate from both oesophageal and gastric cancer. This confusion is due largely to the borderline location between the oesophagus and stomach, the ambiguous use of the term 'cardia carcinoma', and an inability of the current Union Internacional Contra la Cancrum system to classify and stage these lesions. Consequently, the data reported in the literature regarding epidemiology, diagnosis and management are not comparable; it is hardly surprising that the outcome and benefit of surgical resection for adenocarcinoma of the oesophagogastric junction are matters of some controversy[1].

At a recent consensus conference of the International Gastric Cancer Association (IGCA) and the International Society for Diseases of the Esophagus (ISDE) all participating experts agreed that a clear definition and classification of tumours arising in the proximity of the oesophagogastric junction are essential to clarify these inconsistencies[2]. We have defined and described adenocarcinomas of the oesophagogastric junction as tumours that have their centre within 5 cm proximal and distal of the anatomical cardia and have differentiated the following three distinct tumour entities within this area[1,3]:

Type I tumour	Adenocarcinoma of the distal oesophagus which usually arises from an area with specialized intestinal metaplasia of the oesophagus (i.e. Barrett's oesophagus) and which may infiltrate the oesophagogastric junction from above.
Type II tumour	True carcinoma of the cardia arising from the cardiac epithelium or short segments with intestinal metaplasia at the oesophagogastric junction; this entity is also often referred to as 'junctional carcinoma'.
Type III tumour	Subcardial gastric carcinoma which infiltrates the oesophagogastric junction and distal oesophagus from below.

The assignment of a lesion into one of these types is purely morphological and based on the anatomical location of the tumour centre or, in patients with an advanced tumour, the location of the tumour mass. Classification can be performed easily based on a combination of contrast radiography, endoscopy with orthograde and retroflexed view of the oesophagogastric junction, computed tomography and the intraoperative appearance[1,3].

Although all adenocarcinomas arising in the vicinity of the oesophagogastric junction share a number of common epidemiological and morphological features[4], a series of observations in the recent literature provides justification for such a differentiation.

- A preponderance of the male sex is significantly more marked in patients with type I tumours than in those with type II or III tumours (*Table 1*).
- Patients with type I tumour are more likely to a have hiatal hernia and a long history of gastro-oesophageal reflux disease, compared with patients with type II or III tumours (*Table 1*).

Table 1 Epidemiological and morphological characteristics of the three differentiated tumour entities arising in the vicinity of the oesophagogastric junction

	Type I tumour (adenocarcinoma of the distal oesophagus) $n = 308$	Type II tumour (true carcinoma of the cardia) $n = 228$	Type III tumour (subcardial gastric cancer) $n = 279$
Mean age at presentation (years)	60·9	60·2	62·0
Sex ratio (M:F)	8·2:1	5·1:1	2·4:1
Hiatus hernia (%)	72	28	21
History of GORD (%)	84	42	29
Prevalence of associated intestinal metaplasia in the distal oesophagus (Barrett's oesophagus) (%)	81	11	2
Prevalence of associated intestinal metaplasia at or below the gastric cardia (%)	75	32	9
Prevalence of G3/G4 (undifferentiated) tumours (%)	51	56	71
Prevalence of tumours with 'non-intestinal' growth pattern (%)	24	34	45
Primary direction of lymphatic spread	↑↓	(↑)↓	↓↓

Data based on an analysis of 815 patients undergoing resection at the Technischen Universität München between 1982 and 1997 (unpublished data). GORD, gastro-oesophageal reflux disease

- Specialized intestinal epithelial metaplasia in the distal oesophagus (so-called Barrett's oesophagus) with subsequent development of progressively severe dysplastic changes has been clearly identified as the main precursor lesion for adenocarcinoma in the distal oesophagus; it can be found in more than 80 per cent of patients. Although type II and III tumours may also arise from short segments of intestinal metaplasia at or below the gastric cardia[4], this appears to happen in less than 40 per cent of patients with carcinoma of the cardia and in less than 10 per cent of those with subcardial carcinoma. Furthermore, in contrast to specialized intestinal metaplasia in the distal oesophagus, dysplasia seems to be an infrequent phenomenon in areas of intestinal metaplasia at or below the cardia[5,6] (*Table 1*).

- There appear to be marked differences in the frequency of undifferentiated tumours and tumours with a 'non-intestinal' growth pattern (*Table 1*), the expression of cytokeratins[7], and prevalence and type of *p53* mutations[8] reported for adenocarcinomas located above, at or below the gastric cardia.

- Lymphographic studies show that the main lymphatic pathways originating in the lower oesophagus advance both cephalad into the mediastinum and caudad along the coeliac axis, while those from the gastric cardia and subcardial region preferentially make their way to the coeliac axis, the splenic hilum and the para-aortic lymph nodes[9]. This is reflected in the different patterns of lymphatic spread of the various tumour entities that occur at the oesophagogastric junction[1,10,11].

These observations indicate a possible heterogeneity in the pathogenesis and biological behaviour of adenocarcinomas arising in the proximity of the oesophagogastric junction. This clearly calls for further study. The differentiation into tumours of the distal oesophagus (type I), true carcinoma of the cardia (type II) and subcardial carcinoma (type III) provides a classification system for studying these mechanisms in more detail; this should allow comparison of data between various centres and facilitate the choice of surgical therapy. All experts at the recent IGCA–ISDE consensus conference agreed that the classification outlined above should form the basis for defining, assessing and reporting treatment of adenocarcinoma arising in the vicinity of the oesophagogastric junction[2].

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Review

The *p53* tumour suppressor gene

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Background Abnormalities of the *p53* tumour suppressor gene are thought to be central to the development of a high proportion of human tumours. This article reviews current understanding of its function and potential clinical significance.

Methods Material was identified from previous review articles, references cited in original papers, a Medline search of the literature over the 12 months to January 1998, and by scanning the latest issues of relevant journals.

Results and conclusion *p53* is considered to be a stress response gene, its product (the p53 protein) acting to induce cell cycle arrest or apoptosis in response to DNA damage, thereby maintaining genetic stability in the organism. These functions are executed by a complex and incompletely understood series of steps known as the 'p53 pathway', part of which involves induction of the expression of a number of other genes. As *p53* is the most commonly mutated gene in human cancer, it has attracted a great deal of interest as a prognostic factor, diagnostic tool and therapeutic target. However, despite many promising studies, its potential in practical cancer management has still to be realized.

In recent years the rather prosaic term 'p53' has reached the attention of most clinicians but many have only the haziest notion of what it represents. Molecular biologists now believe that the p53 protein has a major role in cellular function and homoeostasis, and that defects in the system to which it is central occur in most if not all human cancers. Its importance is reflected in over 9000 p53-related papers published since 1992. The purpose of this article is to provide an explanation of current understanding of the physiological and clinical significance of p53. Given the size of the literature an exhaustive review has not been attempted; references have been restricted to key articles and representative examples where work has been replicated.

Oncogenes and tumour suppressor genes

The development of cancer is now seen as a complex, multi-step process which depends on both external carcinogenic influences and subcellular genetic defects. The genetic defects may be caused directly by mutagenic carcinogens, but they may also be inherited or may occur sporadically (perhaps induced by background radiation). Indeed, not all carcinogenic stimuli produce mutations; they may merely enhance cellular proliferation or survival such that the likelihood of a dangerous mutation occurring and persisting is increased. It is generally accepted, however, that genetic mutations are necessary before cancer can arise[1].

The genes that are associated with the development of malignancy when dysfunctional are broadly categorized as oncogenes, or tumour suppressor genes. Although this classification may be imperfect, it is a useful means of thinking about the genetic basis of cancer.

Oncogenes

Oncogenes were first identified when it was realized that the tumorigenicity of many retroviruses could be attributed to specific genes, and the first of these to be cloned was v-*src* from the Rous sarcoma virus which causes sarcomas in chickens. It was then discovered that chicken DNA contains a very close relative of v-*src*, and that similar versions of the same gene are present in the DNA of other vertebrates[2,3]. Thus it was realized that the retroviral genes which can transform normal cells into cancer cells (i.e. oncogenes) are actually derived from normal cellular genes. These normal genes are now known as proto-oncogenes, and may become oncogenes either by incorporation of a retrovirus into the genetic material or, more commonly, by mutation at their normal site of residence within the cellular DNA.

Because an oncogene by definition confers malignant properties onto a cell, mutation of a proto-oncogene generally results in gain of function; this may occur by amplification where the affected gene overproduces a protein that drives cell proliferation or enhances survival, or it may occur by production of a mutant protein which escapes control mechanisms that normally constrain its proliferative activity. It follows that proto-oncogenes encode proteins that stimulate cellular growth or survival. These may be broadly categorized as growth factors, growth factor receptors, intracellular signal transducers (which transmit the signal from an activated receptor to the nucleus) and transcription factors (which induce protein synthesis by stimulating the DNA in the nucleus to produce messenger RNA).

An oncogene (i.e. a mutated proto-oncogene) typically acts as a dominant gene, and so a mutation in one allele will be sufficient for it to become manifest. However, with few exceptions[4], oncogenes are not inherited and usually contribute to the pathogenesis of cancer by somatic mutations within the cells of the target tissues.

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Tumour suppressor genes

In contrast to oncogenes, tumour suppressor genes, in their normal state, encode proteins that act to maintain cell numbers by suppressing proliferation or promoting loss. These genes become involved in the tumorigenic process when they sustain mutations that result in loss of function. In this case the normal gene tends to act in a dominant fashion and only when both alleles are damaged will the effect of the mutant gene be apparent. Because of this, mutations in single alleles of tumour suppressor genes may be passed through the germline; virtually all of the genes that have been identified as responsible for inherited cancer belong to this category[1]. Sporadic loss of tumour suppressor function in a genetically normal individual can and does occur but, as this requires both alleles in a single cell to malfunction due to either mutation or deletion (loss), it occurs much less frequently than in an individual who has an inherited defect in all cells.

p53 belongs to the category of tumour suppressors and it appears to occupy a pivotal role in deciding the fate of cells that have been stressed. Thus elimination of cells that have sustained genetic damage depends on functional p53, and damage to the *p53* gene itself may allow cells bearing other mutant genes to proliferate unchecked.

Physiological role of p53

p53 is a phosphoprotein made up of 393 amino acids; it resides in the nucleus of the cell. It was first discovered as a protein that could bind with the virally encoded large 'T' antigen (or protein) which is responsible for the transformation of cells by simian virus 40[5,6]. These early studies were attempting to understand the mechanism by which this T antigen exerted its transforming properties by searching for cellular proteins that might be directly affected. Antibodies raised against the large T antigen immunoprecipitated a protein of 53 kD (hence the term 'p53') and for several years this protein was thought to be the product of an oncogene. It was later recognized, however, that many transformed cells contained *p53* gene mutations and that normal (or 'wild-type') p53 functioned to suppress cellular proliferation.

It is now established that the p53 protein is central to the cellular response to a wide variety of stressful stimuli[7,8]. These stimuli, which include DNA damage, hypoxia, heat shock, metabolic changes and certain cytokines, activate the p53 protein, which in turn drives a series of events that culminate either in cell cycle arrest or apoptosis (programmed cell death). This is illustrated in *Fig. 1*; it can be appreciated that disruption of the p53 pathway significantly affects the ability to repair or discard a damaged cell, which can then go on to replicate. If this cell has sustained damage to one or more proto-oncogenes or to other tumour suppressor genes, a cancer may result.

So one of the physiological roles of p53 is to prevent the formation of tumours and, if this hypothesis is correct, damage to the *p53* gene itself would predispose to tumour formation. As will be obvious from the following section, considerable evidence has accumulated to support this view, explaining the recent phenomenal interest in this protein. However, from an evolutionary point of view, it would be surprising if this were the only function of p53.

Tumours with p53 abnormalities tend to occur in old age and do not affect animals in their reproductive phase. However, studies using 'knockout' mice (in which specific genes have been inactivated) have shown that p53 null mice, while viable, display a high rate of developmental abnormalities, especially of the nervous system[9,10]. This suggests that p53 might protect against teratogenesis and experiments using benzo[a]pyrene have shown increased teratogenicity in p53 null mice[11]. In addition, after *in utero* irradiation p53 null mice have a high incidence of anomalies and a low death rate, whereas normal mice have a low incidence of anomalies and a high death rate[12]. Thus p53 may have evolved primarily as a suppressor of teratogenesis, with tumour suppression being a secondary property; it has been suggested that it may have an even more fundamental role as a facilitator of developmental complexity in higher animals[13].

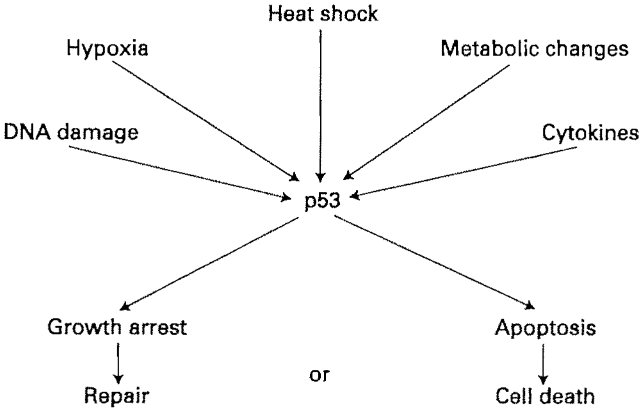

Fig. 1 Diagrammatic representation of the central role of p53 in the coordination of the cellular response to various stresses

Control of p53 and the 'p53 pathway'

As indicated in *Fig. 1*, p53 is thought to act as a nodal point between stressful stimuli and the final fate of the cell, and multiple events occur both 'upstream' and 'downstream' of p53 induction. Under normal circumstances cells contain very low levels of p53 protein, but stressful stimuli trigger 'upstream' events that lead to the accumulation or activation of p53[7,8] which then triggers the 'downstream' pathway. A graphic illustration of the upstream pathway in action is provided by the rapid appearance of immunodetectable levels of p53 in the epidermis and superficial dermal fibroblasts of normal adult human skin when exposed to doses of ultraviolet irradiation sufficient to cause mild sunburn[14] (*Fig. 2*).

As mentioned above, various forms of stress initiate the upstream pathway and, although the components of the pathway (i.e. the signals that communicate with p53) have not been identified, it is likely that protein kinases which are activated by DNA damage and subsequently phosphorylate p53 may be responsible[15,16]. As one end-result is increased expression of p53, it might seem reasonable to suppose that the upstream signals cause increased transcription and subsequent translation of the *p53* gene. There is, however, little evidence to support this hypothesis and other mechanisms must be invoked. Another nuclear protein, mdm-2, appears to be crucial in the control of p53 and has a key role in the observed accumulation of p53 in response to stress.

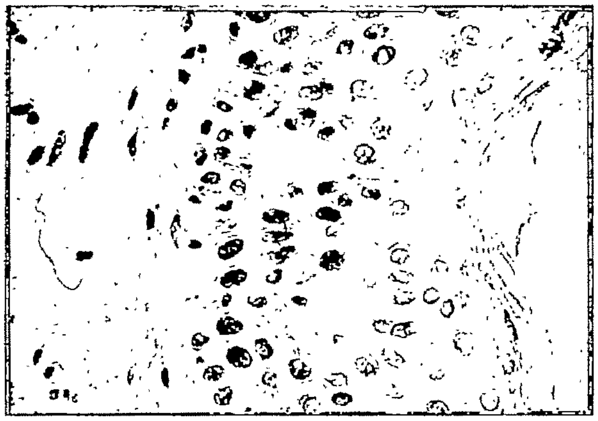

Fig. 2 Human skin immunostained for p53 protein after exposure to sufficient ultraviolet irradiation to cause mild sunburn. The dark staining indicates overexpression of p53 in the nuclei

Mdm-2 is a 491-amino-acid phosphoprotein which can bind to p53[17]; it not only blocks its biological activity, but also targets p53 for destruction via the ubiquitin proteosome pathway[18,19]. Mdm-2 may be thought of as a component of the downstream pathway as its transcription is increased by p53[20] (*Table 1*) and it thereby acts as a negative feedback mechanism controlling p53 levels (*Fig. 3*). That this is vitally important has been illustrated by knockout experiments showing that mdm-2 null mice are not viable unless they are also null for p53, indicating that mdm-2 is necessary to prevent unregulated p53 activity[21].

On the basis of these findings it is possible to speculate that mdm-2 may be important in controlling the response of p53 to stress, and that phosphorylation of mdm-2 or p53 itself by stress-activated protein kinases could prevent their interaction and hence allow accumulation of p53[22,23]. Certainly other influences that affect the survival of cells may act through mdm-2, as evidenced by the finding that basic fibroblast growth factor induces mdm-2 independently of p53 and so renders the cell insensitive to stimuli that would normally trigger apoptosis through the p53 pathway[24].

Table 1 Key genes transcriptionally activated by p53 which mediate the pathway leading to cell cycle arrest or apoptosis

Gene	Function of gene product
mdm-2	Binds to and inactivates p53, forming an autoregulatory loop
p21/WAF1/Cip1	Arrests cell cycle by inhibiting cyclin–cyclin-dependent kinase complexes and binding to PCNA
GADD45	Arrests cell cycle by binding to PCNA
Bax	Promotes apoptosis
IGF-BP3	Enhances apoptosis by blocking the mitotic activity of insulin-like growth factor

PCNA, proliferating cellular nuclear antigen

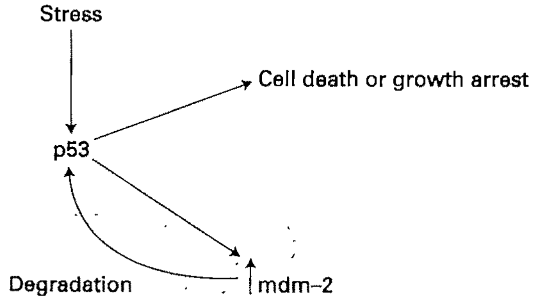

Fig. 3 Diagrammatic representation of the role of mdm-2 in preventing unregulated activation of p53

Whereas the mechanism of the upstream pathway is still largely speculative, the downstream pathway is better understood. p53 is a transcription factor; it can bind to specific DNA sequences and activate the transcription of genes containing such binding sites in their promoter regulatory regions[25,26]. The number of genes thought to be activated in this way is growing rapidly and there is an equally impressive range of genes which seem to have their function repressed by p53[7,27]. Some of the more robust candidates for the downstream p53 pathway are shown in *Table 1*; it can be seen how activation of these genes can affect the cell cycle and the rate of apoptosis. It has become clear, however, that p53 may also act in other ways not related to transcriptional activity. For instance, recent evidence indicates that it may inhibit nuclear DNA replication directly[28] and that p53-dependent apoptosis can occur without transcriptional activation of p53 target genes[29,30].

Despite the vast amount of data now available, it must be stressed that little of the mechanism of p53 function is certain; the accumulation of knowledge in this field is currently very rapid. Recently, homologues (i.e. distinct proteins with shared functions) of p53[31–34] and an mdm-2-related protein (mdm-x)[35] have been described, and these are likely to have important implications. It is possible that the p53 homologues make up a family of molecules with similar effects but induced by different signals and therefore play fundamentally different roles in cellular homoeostasis.

It must also be appreciated that much of our knowlege of p53 function comes from *in vitro* work and that the *in vivo* situation presents a whole new set of problems. In particular, it has become clear that the p53 response varies not only according to the insulting stimulus but also according to the tissue and cell type involved[36,37]. These discoveries, coupled with the increasingly complex interrelated pathways that are emerging, leave room for significant changes in our view of the precise significance of p53 over the next few years.

Role of p53 in cancer

The main reason for the phenomenal recent interest in p53 is the finding that a high proportion of human cancers (up to 50 per cent) contain mutations of the *p53* gene[38] (*Table 2*). Most commonly these genetic changes are missense mutations in one allele, although deletions or chain-termination mutations can occur. The mutational spectra at the *p53* locus indicate that many different environmental mutagens are likely to be involved[8], but these have yet to be identified specifically. The actual site of the mutation is also important; as p53 acts mainly as a transcription factor, mutations in the DNA-binding domain have the greatest effect on function. Most missense mutations in cancers are located in this domain and these lead to the production of p53 protein which fails to bind to DNA in the normal sequence-specific

Table 2 Frequency of *p53* mutations in different human tumour types

Tissue or site	Frequency (%)
Lung	50
Colorectum	50
Oesophagus	45
Ovary	44
Pancreas	44
Skin	44
Stomach	41
Head and neck	37
Bladder	34
Prostate	30
Hepatocellular	29
Brain	25
Adrenal	23
Breast	22
Endometrium	22
Kidney	19
Thyroid	13
Haemopoietic system	12
Carcinoid	11
Melanoma	9
Parathyroid	8
Cervix	7

fashion[39]. In addition, work with knockout mice has shown that p53 null animals display a high rate of tumour formation[40]. It has also been shown that the Li–Fraumeni cancer family syndrome is caused by a germline mutation in the *p53* gene[41,42].

Given the involvement of p53 in the cell cycle arrest or apoptotic response to genotoxic damage outlined above, these findings are not surprising. It is reasonable to suppose that loss of effective p53 would allow damaged cells to survive and open the door to the accumulation of mutations in other tumour suppressor genes and proto-oncogenes. It has been shown in transgenic mice that apoptosis slows the growth of a tumour induced by a T antigen which cannot inactivate p53 function and that rapid tumour growth with reduced apoptosis occurs in p53 null animals with the same antigen[43]. In addition, the p53 mutations found in squamous cell carcinoma are also found in skin lesions caused by ultraviolet radiation, and in p53 null mice ultraviolet light does not cause the typical apoptotic changes seen in the skin of normal mice[44].

However, it is naive to regard *p53* mutation simply as an 'enabling' event in carcinogenesis. While it appears to be an early event in the development of skin cancer[44], in colorectal cancer it has been found to occur late in the adenoma–carcinoma sequence[45]. The timing of a *p53* mutation is related to tumour type and must depend on a complex series of variables. It has been suggested, because p53 is induced by hypoxia, that the need for angiogenesis is balanced by the elimination of p53 function[8]. Thus a rich blood supply early in tumour development may leave *p53* mutation to arise at a later stage.

A key discovery in the oncological significance of p53 was high levels of the protein in many tumours. This accumulation results from an increase in p53 stability, which in turn is usually associated with a mutation in the *p53* gene[46,47], and it was long thought that the mutant protein was inherently more stable than the wild-type protein. However, recent evidence indicates that p53 protein stability depends not specifically on mutation, but on binding to mdm-2[22]. Mdm-2 is transcriptionally activated by p53 and then targets it for destruction, thereby forming an autoregulatory mechanism. It is now believed that mutant p53 cannot activate the transcription of mdm-2 and it is for this reason that p53 accumulates, a hypothesis supported by experimental work which has shown that p53 disappears from human tumour cells microinjected with mdm-2[48].

Detecting mutations in the *p53* gene is both expensive and time consuming, and the discovery that accumulation of the protein is associated with mutation has led to a proliferation of studies of archival material from human tumours using immunohistochemical detection of p53 as a surrogate for mutation. Because p53 acts as a protective mechanism against the perpetuation of genetic damage, it has been suggested that tumours with functioning p53 may carry a better prognosis than those expressing the mutant protein. In support of this theory there are numerous studies that have demonstrated an association with poor survival and accumulation of p53 in breast cancer[49,50], colorectal cancer[51–53], gastric cancer[54], lung cancer[55], ovarian cancer[56] and several other tumour types. However, there are a number of studies that have not shown this association and it has been concluded that any adverse prognostic effect is probably small[57]. Indeed, recent studies on colorectal and breast cancer using robust reagents have not been able confirm any prognostic significance of p53 accumulation even with a large number of patients[58,59]. This is perhaps not surprising as the fact that malignant transformation has already occurred indicates a fundamental breakdown of cellular control, and there is no good *a priori* reason why if a *p53* mutation has or has not contributed to this process the outcome should be any different.

It is also important to appreciate the limitations of using immunohistochemical detection of p53 as a marker of p53 function. First, it has been shown that detectable expression of p53 can occur in the absence of gene mutations[60,61]. This may be due to increased sensitivity of modern reagents, but other explanations such as malfunction of mdm-2 may apply in some instances. Second, it is conceivable that some mutations may not interfere with mdm-2 transcription and therefore remain susceptible to the controls exerted on the wild-type protein but still be functionally inactive. Third, it is recognized that viral proteins, such as the E6 human papilloma virus protein, can target wild-type p53 for destruction in a similar way to mdm-2[62].

Most important, however, is the concept that it is the p53 pathway that is crucial rather than the protein alone. Some *p53* mutations may have a different downstream effect from others; for example, some mutants can activate the *p21* gene but not the *bax* gene[63] so that the effects on cell cycle arrest may be different to those on apoptosis. Furthermore, rather than sustaining *p53* mutations some tumours, especially sarcomas, inactivate p53 by overexpression of mdm-2[64]. Very recently another tumour suppressor, p33 (encoded by the *ING1* gene), has been shown to be obligatory for the cell cycle inhibitory effects of p53[65] and it may also cooperate in the initiation of apoptosis. So if p33 is necessary to support the anti-tumour effects of p53, mutations in the *p33/ING1* gene will have to be taken into account. The p53 pathway is complex and not fully understood. It is possible that most, if not all, tumours have sustained some damage to this mechanism, but this can be detected by conventional methods only if the *p53* gene itself is mutated and consequently overexpressed.

Potential role of p53 in the management of cancer

Prognostic factor

p53 analysis does not appear to have any clinically significant utility as a prognostic factor and is unlikely to supplant conventional factors, such as stage and histological grade, in the near future. However, there is great interest in the significance of p53 in modulating the response to radiotherapy and chemotherapy. As both of these forms of cancer treatment cause DNA damage, it is reasonable to assume that p53-dependent apoptosis may be responsible for at least part of the therapeutic effect and there is evidence to support this hypothesis. Cells transformed by the viral oncogene *E1A* undergo p53-dependent cell death in response to ionizing radiation or treatment with 5-fluorouracil, etoposide or doxorubicin[66]. Work using transgenic mice has shown that *p53* mutations increase the resistance of haemopoietic cell lineages to γ irradiation[67]. In addition, X-irradiation at 9·5 days of gestation produces fewer deaths but more embryonic abnormalities in p53-deficient mice compared with wild-type animals[12], reinforcing the notion that normal functioning of the p53 pathway is required for efficient DNA repair or cell death after irradiation.

Study of a small series of patients with rectal cancer showed that radiotherapy appeared to increase the number of apoptotic cells only in tumours expressing wild-type p53[68]. In breast cancer *p53* mutations are well correlated with resistance to doxorubicin treatment[69]. It is also of interest that human tumours that are generally sensitive to radiotherapy or chemotherapy, such as testicular cancer or childhood acute lymphoblastic leukaemia, display low rates of p53 mutations[66,70], whereas tumours that often contain *p53* mutations, such as colorectal and lung cancers, tend to respond less well to chemotherapy or radiotherapy.

The use of *p53* mutation analysis to predict sensitivity to potentially toxic therapy is therefore an attractive proposition, but there is some evidence to suggest that p53 status may not always predict outcome reliably. Some reports indicate that inactivation of the *p53* gene can actually render cells more sensitive to genotoxic damage[71,72], and in a study of human squamous carcinoma cells *p53* mutations did not correlate with radiosensitivity[73]. This is an area that requires large-scale clinical studies with careful assessment of p53 function.

Diagnostic tool

The fact that *p53* mutations are expressed by so many human tumours has led to attempts to use them for diagnostic purposes. In cytology, suspicious cases frequently occur for which a satisfactory distinction between benign and malignant cannot be made, and immunocytochemical detection of p53 has been used in a wide variety of tumours[74]. As *p53* mutation is not a consistent finding in all tumours, the sensitivity of this approach is poor, but the specificity is high (in the region of 97 per cent) and staining for p53 in suspicious cytology specimens may prove to be a useful adjunct to morphological assessment.

Another area in which *p53* mutations have been used in an attempt to improve diagnosis is faecal screening for gastrointestinal cancer. As *p53* is one of the genes that is commonly mutated in colorectal cancer, it has been proposed that detection of *p53* mutations along with a panel of other mutated genes might offer a useful screening tool. However, while *p53* mutations can be detected in gut lavage fluid from patients with colorectal cancer[75], effective faecal tests have proved elusive owing to difficulties in extracting appropriate DNA from stool.

Finally, there has been interest in looking for mutant DNA in blood as a marker for minimal residual disease after apparent eradication of primary malignancy[76]. If this were feasible, it might prove useful for selecting patients for adjuvant therapy and for monitoring treatment. The *p53* gene is an obvious candidate for this approach, although little real progress has been made in this direction.

Therapy

In the treatment of cancer, restoration or modulation of p53 function has become something of a holy grail, based on the premise that the tumour cells lacking this function might destroy themselves or at least become more susceptible to the effects of DNA damage inflicted by conventional chemotherapy or radiotherapy. Essentially, three main approaches look promising in this field. First, there is virus-mediated gene transfer in which a viral genome is engineered to contain foreign genes which are expressed in the host cell genome after infection. Second, there is the use of a cytolytic virus which can replicate only in cells that lack p53 function, and by targeting such cells could destroy tumours with mutant p53. Third, there is the discovery or design of small molecules that can interfere with the negative regulation of p53, pharmacologically activating the p53 response.

Virus-mediated gene transfer. A wild-type *p53* DNA fragment has been inserted into a retrovirus (LNSX retroviral vector). Using this to restore the wild-type *p53* gene to lung cancer cells, it has suppressed the growth of both lung cancer cell lines and human lung cancers in nude mice[77,78]. Similar findings in colorectal cancer cells lines have been reported using the replication defective adenovirus Ad5/CMV/p53[79]; it has also been shown that this agent has a synergistic effect when used with cisplatin chemotherapy[80].

There is one reported clinical trial using wild-type *p53* gene transfer in nine patients with non-small cell lung cancer in whom conventional treatment had failed. In this study the LNSX retroviral vector was injected directly into the tumour either percutaneously with radiological guidance or via a bronchoscope[81]. *In situ* hybridization and DNA polymerase chain reaction showed vector–*p53* sequences in post-treatment biopsies, and apoptosis was more frequent in post-treatment than in pretreatment biopsies. No treatment-related toxicity was noted and tumour regression occurred in three patients. Further extensive trials of adenovirus encoding wild-type p53 are currently underway.

Cytolytic virus therapy. The DNA tumour virus adenovirus produces a 55-kDa protein from the *E1B* region of its genome which binds and inactivates p53. It was hypothesized that an adenovirus lacking E1B would not be able to replicate in normal cells but would in cancer cells lacking p53 function. For this reason, ONYX-015, an *E1B* gene-attenuated adenovirus was compared with normal adenovirus in human and colonic cancer cell lines with and without p53 function. As expected, the ONYX-015 virus replicated as efficiently as the normal virus in the cell line lacking wild-type p53, but not in the line with normal p53 function[82].

Subsequent work showed that, while normal human cells are very resistant to the cytolytic effects of ONYX-015, a wide range of human tumour cell lines with either mutant or normal *p53* gene sequences is destroyed[83]. It is interesting that tumours with wild-type p53 are susceptible; this is presumably due either to the presence of undetected *p53* mutations or to malfunction of other components of the p53 pathway (e.g. mdm-2 overexpression). A phase I trial of ONYX-015 in patients with advanced cancer is currently underway and a report should be forthcoming in the near future.

Interference with the negative regulation of p53. The activity of p53 is dependent, at least in part, on sequence-specific DNA binding and this process is controlled by a negative regulatory domain in the p53 molecule[84,85]. Neutralization of this domain by a specific antibody activates p53[86] and it is likely that stress-related factors which influence the transcriptional activity of p53 act in a similar way. The same antibody can activate mutant forms of p53 synthesized by human tumour cells lines[87], and this opens up the possibility of discovering or designing small molecules that could activate mutant forms of p53, thereby rescuing p53 function. Similarly, the discovery that mdm-2 interacts with p53 via a small molecular interface to block p53 function suggests that small molecules could be used to disrupt this interaction[22]. This would be particularly useful in tumours, especially sarcomas, in which p53 is normal but where there is overexpression of mdm-2[64].

Conclusion

p53 research is tantalizingly close to revolutionizing clinical practice in oncology, but it still has some way to go. The prognostic significance of p53 is uncertain, its role in diagnosis is promising but yet to be developed, and its potential in therapy is just emerging. However, there is no doubt about the central role of p53 in the development of cancer and one of the main questions to answer is: Why do a significant proportion of tumours seem to have normal p53? The answer may come from intensive study of the p53 pathway rather than of p53 in isolation, as it is conceivable that all malignant tumours have a defect somewhere along this pathway. This is the direction being taken in oncologically relevant p53 research and, when the pathway and its defects are fully understood, the tailoring of therapy for an individual tumour based on its molecular and genetic profile will be a practical strategy.

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Review

Association between breast and colorectal cancers

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Background The risk of breast and colorectal cancers in immigrants from non-industrialised countries is sharply increased when they adopt a Western lifestyle. In addition, epidemiological studies on Western populations show an association between the two tumours, both in the same individual and also in close relatives. Most studies agree that high energy intake, obesity and inadequate physical exercise are associated with an increased risk of both tumours.

Methods Risk markers for each cancer are examined in order to identify causative nutritional factors or metabolic–endocrine dysfunction. The role of steroid hormones and other possible carcinogenic mechanisms is discussed, concentrating on evidence of a role for insulin and insulin-like growth factors (IGFs) in the promotion of carcinogenesis in both organs.

Results Individuals with a genetic susceptibility to insulin resistance show triggering of hyperinsulinaemia following excessive weight gain or long-term diet high in saturated fat. Case–control studies show an association between hyperinsulinaemia and evidence of breast or colorectal carcinoma. Multiple laboratory studies show that increased activity of IGFs can stimulate the growth of human breast and colorectal cancer cells.

Conclusion It is postulated that either insulin resistance and its concomitants promote the development of breast and colorectal cancers, or that they share common risk factors. Sex steroid metabolism and organ specificity may explain age and sex differences between the tumours in relation to the role of obesity. Recent research suggests that a diet high in *n*-3 polyunsaturated fatty acids may reduce the risk of developing insulin resistance. This observation may be applied to test the hypothesis that an effect on hyperinsulinaemia may modify the risk of developing breast or colorectal cancer.

Breast and colorectal cancers develop in the same patient more commonly than would be expected by chance[1], suggesting that the cancers share either genetic or environmental factors in their aetiology. The relatives of patients with breast cancer are also reported to be at increased risk of developing both breast and colorectal cancers[2,3]. Pooled results from seven cohort studies showed a weak association between breast cancer and subsequent risk of colorectal cancer, while those from five cohort studies showed a weak association between colorectal cancer and subsequent risk of breast cancer[4]. Pooled results from five case–control studies showed a positive association between breast cancer and colorectal adenoma[4].

Both breast and colorectal cancers are likely to involve interaction between genetic and environmental factors. DNA-based screening is now available for hereditary breast ovarian cancer, hereditary non-polyposis colonic cancer (HNPCC) and for Gardner syndrome (polyposis coli)[5]. So far, however, genetic linkage has not been shown in the susceptibility of women to breast and colorectal neoplasms. HNPCC is characterized by early onset of cancers of the colon and endometrium, together with increased incidence of other cancers affecting the ovary, and gastrointestinal and urological tracts, but the inclusion of breast cancer in this syndrome is controversial[6].

The aetiological importance of environmental and lifestyle factors in breast and colorectal cancers is suggested by correlation of higher socioeconomic status with their risk[7], and by their marked increase in Asian populations taking up residence in Western countries[8]. Differences in incidence rates between countries have led to estimates that 90 per cent of colonic cancers and 80 per cent of breast cancers are related to environmental factors[9]. A low-fat, high-fibre diet is likely to be protective but such advice is not sufficiently specific. Evidence that certain vitamins, antioxidants, selenium or calcium are protective is inconclusive[1].

A recent ecological study suggests .that the cancer-promoting effects of animal fat might be opposed by fish oil in the diet[10]. Risk of breast and colorectal cancers in 24 European countries showed a positive association with total and animal fat intake, but also an inverse association with fish and fish oil consumption expressed as a proportion of total fat intake. The study showed (a) significant correlation for both male and female colorectal cancers and for female breast cancer, (b) a protective effect of fish and fish oil confined to countries with a high animal fat intake (over 85 g per head daily), and (c) significant correlation not only with current dietary intake but also with intake 10 or 23 years before death from cancer[10].

Relevant to these observations are studies detailed below, which focus on the role of polyunsaturated fatty acids in the growth of animal models of mammary and colonic cancers[11–19]. They show that while *n*-3 polyunsaturated fatty acids (and foods rich in these, such

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as fish oil and perilla seed vegetable oil) have an inhibitory effect on carcinogenesis, the *n*-6 group of fatty acids (and foods rich in these, such as corn oil) have a promoting effect.

The ratio of saturated to unsaturated fatty acids in the diet has been related to insulin levels in the human[20]. Immigrants to the UK belonging to races with a genetic susceptibility to insulin resistance show triggering of hyperinsulinaemia by a diet high in animal fat, excessive weight gain and inadequate physical exercise[21–24]. This review postulates that hyperinsulinaemia can increase the risk of both breast and colorectal cancers in Western populations, and that the increased risk of these cancers in immigrants from non-industrialized countries is due more to adoption of the Western lifestyle than to environmental carcinogenic factors. The evidence is indirect and focuses mainly on nutritional factors.

Dietary constituents and risk of breast and colorectal cancers

The long-standing hypothesis that high fat intake, and animal fat in particular, increases breast cancer risk is based on animal studies and correlation with international per capita fat intake[25]. There is, however, little evidence of a positive association between individual fat intake and breast cancer risk[1]. It is agreed that dietary questionnaires in most studies relate to total fat intake during adult life and that an influence by fat intake in childhood cannot be excluded[1,25]. Most case–control studies have suggested that higher intake of fibre, vegetables and fruit protect against breast cancer[26], but this has not been confirmed in prospective studies[27,28]. Recent case–control studies conclude that monounsaturated fatty acids such as olive oil protect against breast cancer[29–31], while several ecological studies suggest that high intake of fish and fish oil products is protective[10,32,33].

In the case of colorectal cancer, most epidemiological studies indicate that high animal fat intake is positively associated with risk, whereas vegetable consumption is protective[1]. Ecological studies[10,34], case–control studies[35–37] and a prospective study[38] suggest a protective effect by fish and fish oil consumption against colorectal cancer. Evidence of a protective effect by the high calcium levels in dairy products is less certain[39].

Biological mechanisms to explain these dietary associations are unclear; in the case of breast cancer most are based on the oestrogen hypothesis. A high fat intake is postulated to increase oestrogen levels in postmenopausal women by greater aromatization in the excess fat deposits. On the other hand, a high fibre intake is thought to reduce oestrogen levels both in premenopausal and postmenopausal women by decreasing absorption of oestradiol formed in the colon[40]. Dietary supplements of wheat bran (but not oat or corn bran) have been shown to reduce serum oestrogen levels in premenopausal women[41]. This has been ascribed to a reduced colonic transit time[42].

In the case of colonic cancer, higher fat intake is postulated to increase bile acid concentration in the bowel and also the growth of colonic bacteria which convert bile acids into carcinogens[43]. Soluble fibre (found in fruit, vegetables and grains such as oats) is thought to reduce production of short-chain fatty acids by bacterial fermentation, while insoluble fibre (found in grains such as wheat and rice) is said to increase faecal bulk and thus reduce colonic transit time[44].

A role for polyunsaturated fatty acids in promoting carcinogenesis in the breast and colon has been suggested by a series of studies in animal models. Growth of chemically induced mammary cancer in rats is promoted by *n*-6 fatty acids, while *n*-3 fatty acids have an inhibitory effect[11]. Studies on human mammary cancer cell lines *in vitro* show that *n*-6 fatty acids stimulate growth, whereas *n*-3 fatty acids inhibit growth[12], and similar effects occur on the growth and metastasis of human mammary cancer explants in nude mice[13]. In the case of chemically induced colonic cancer in rats, growth is promoted by high animal fat intake[14] but inhibited by a diet rich in *n*-3 fatty acids in the form of fish oil[15], perilla seed vegetable oil[16] or long-chain *n*-3 fatty acid derivatives[17]. In addition, premalignant epithelial hyperplasia in the rat colon may be normalized by feeding vegetable oils rich in *n*-3 fatty acids[18,19].

The *n*-3 and *n*-6 fatty acids are not synthesized in the tissues but are derived mainly from marine animal or dietary seed oil sources. They are incorporated into cell membrane phospholipids and control the passage of nutrients, hormones and cell signals. On this basis, it has been postulated that they modulate the production of prostaglandins, and possibly influence tumour growth in this way. Membrane fatty acid composition has been shown to reflect dietary intake of polyunsaturated fatty acids, and fish oil supplements to adult women on a low fat diet have been shown to increase the ratio of *n*-3 to *n*-6 fatty acids in plasma and breast adipose tissue[45].

Postulated role for hyperinsulinaemia

A link has been proposed between the aetiology of insulin resistance and that of breast cancer, and it has been proposed that interaction between glucose metabolism and ovarian hormones may influence tumour growth[46]. The hypothesis has been supported by the findings in case–control studies that hyperinsulinaemia is a risk marker for postmenopausal breast cancer[47–51]. In the case of colorectal cancer too, an association with insulin resistance is reported[49,51,52]. Another study notes an association with abdominal obesity which is generally assumed to be related to insulin resistance[53]. The same study notes obesity and diet to be independent factors in increasing the risk of colonic carcinoma and adenoma.

In adults, fasting insulin levels are higher with a higher saturated fatty acid content in the diet, whereas a higher fish intake rich in *n*-3 fatty acids is protective[21,22]. In obese pubertal children, insulin levels are lower in those with higher plasma levels of *n*-3 fatty acids[54] but higher in those with higher *n*-6 fatty acid levels[55]. The observations in adults and children suggest that the high *n*-6:*n*-3 fatty acid ratio in the typical Western diet can favour a higher insulin level.

The onset of menarche is physiologically accompanied by the manifestation of insulin resistance but its persistence after menarche is strongly influenced by the fatty acid profile of the diet[56]. The presence of hyperinsulinaemia can lead to abnormal ovarian steroid steroidogenesis in adolescent girls[57] and the abnormal steroid profile is likely to be a factor in determining subsequent breast cancer risk[46].

Hyperinsulinaemia increases circulating levels of insulin-like growth factor (IGF) 1 and, by decreasing the production of IGF-binding proteins, may further increase the level of free IGF-1 available to the tissues[58]. IGF-1 is thought to have a major role in promoting carcinogenesis[59]. In addition to an endocrine effect by the circulating IGF-1, stromal fibroblasts have been shown to produce IGF-1 and IGF-2, which may act synergistically with oestrogen and exert a paracrine effect in promoting mammary carcinogenesis[60]. A recent study on normal human breast tissue xenografts in nude mice reports that oestradiol may reinforce the mitogenic affects of IGF-1 by upregulating the IGF-1 receptor[61].

In the case of colonic cancer, too, a link has been postulated between the aetiology of insulin resistance and that of the tumour, proposing also that the presence of hyperinsulinaemia may increase the risk of colonic cancer[53]. Aberrant crypt foci in the colon, regarded as an early stage in carcinogenesis, can be induced in rats by feeding azoxymethane; their growth is decreased by feeds with a high *n*-3 fatty acid content[19,62]. In patients with sporadic colonic adenoma, proliferative activity in the rectal mucosa is reduced by fish oil dietary supplements[63], and in patients with colonic cancer with high proliferative activity in the bowel mucosa a similar effect occurs from *n*-3 fatty acid supplements[64].

Insulin can stimulate growth in human colonic cancer cell lines[65,66] and, as noted above, hyperinsulinaemia increases the level of free IGF-1 available to the tissues. Studies on human colonic cancer specimens and cell lines suggest a possible role for IGF-1 and its receptor in the stimulation of colonic cancer growth. So IGF-1 receptors have been demonstrated in both normal and malignant human colonic epithelium[67], and both IGF-1 and IGF-2 have been shown to increase proliferative activity in colonic cancer cell lines via the IGF-1 receptor[68]. Recent research has shown that IGF-binding proteins can modulate the effect of IGF-1 on the growth of normal and malignant colonic epithelium and determine whether cell growth is promoted or inhibited[69,70].

Postulated role for weight gain

Most case–control studies agree that an increased risk of breast, colorectal, endometrial or prostate cancer is associated with a high body mass index at the time of diagnosis. The promotion stages in carcinogenesis usually extend over many years and evaluation of the role of body mass needs to consider adiposity (weight adjusted for height), timing of weight gain, pattern of fat distribution and concomitant metabolic–hormonal changes[71,72].

A critical body fatness is likely to trigger the onset of menarche[73] but obesity in childhood is not associated with increased breast cancer risk[74]. Obesity in premenopausal Western women is usually associated with a decreased breast cancer risk, but a recent large prospective study in the USA found that this applied to excessive weight gain before the age of 18 years but not if it occurred later[75]. Experimental evidence suggests that susceptibility of mammary tissue to carcinogenesis is greatest in early adult life and it has been postulated that hyperinsulinaemia associated with weight gain starting in adolescence may modify ovarian steroid synthesis[76]. In the case of postmenopausal women, on the other hand, most studies agree that increased breast cancer risk is associated with a high body mass and, in the American prospective study[75], increased risk was found to relate to all weight gain after the age of 18 years. The study confirms that the timing of weight gain is critical in determining the relative risks of premenopausal and postmenopausal breast cancers.

With regard to colorectal cancer, case–control studies on the association of obesity with cancer risk provide inconsistent results[77]. A large prospective study showed a weak positive association in men but not in women[78]; this was confirmed recently in a similar study which found increased risk in men who were more than 40 per cent overweight but not in women[79]. An individual's age at the time of weight gain may be important, as demonstrated by reports that a history of being overweight in adolescence or young adult life is a more powerful predictor of colonic cancer risk than is being overweight at the time of diagnosis[80,81].

Abdominal distribution of obesity and decreased physical activity are reported to be markers of increased colonic cancer risk in men, and these characteristics are assumed to reflect insulin resistance and hyperinsulinaemia[53]. It has been suggested that the Western lifestyle favours a positive energy balance and that both energy intake and physical activity can affect colonic cancer risk through metabolic mechanisms. Reports that the effect of a high fat diet on colonic cancer promotion can be modified by physical activity are, however, not consistent[1]. The Physicians' Health Study in the USA has found that physical activity is not inversely related to colonic cancer risk in either obese or non-obese men[82].

Conclusion

A high intake of animal fat is associated with increased risk of both breast and colorectal cancers, but epidemiological studies to date have not identified specific fatty acids that promote or protect from each tumour. Dietary factors in childhood may be more important in the development of breast than colorectal cancer, as suggested by reports that Japanese immigrants to the USA have an increased rate of colonic cancer in the migrating generation itself, whereas breast cancer rates take several generations before they approach those of the general population[8].

There is increasing epidemiological and biological evidence that risk for both tumours is associated positively with hyperinsulinaemia, a feature that is favoured by a high fat diet and excessive weight gain. The association of obesity with cancer risk shows age and sex differences between the two types of cancer; this may reflect differences in sex steroid metabolism or organ specificity. This review postulates that either insulin resistance and its concomitants promote the development of breast and colorectal cancers, or else that they share common risk factors.

There is considerable evidence that a diet high in saturated fat increases the risk of hyperinsulinaemia, and animal data suggest adverse effects from *n*-6 unsaturated fatty acids but protective effects from *n*-3 fatty acids derived from fish or seed oils. This observation may be used to test the hypothesis that an effect on hyperinsulinaemia may modify the risk of developing breast and colorectal cancers.

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Review

Traumatic and septic shock alias post-trauma critical illness

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Background The mortality associated with septic shock, both in percentage of septic shock cases and total number of septic shock cases, has been increasing over the past several decades. This is despite major advances in diagnosis and treatment. The basic cause of traumatic and septic shock has been only partially elucidated.

Methods Data sources include research papers on the subject of traumatic and septic shock from 1875 to the present. These papers numbered over 10 000, few of which are included in the reference list because many are duplicative or negative. Over 1000 articles were reviewed which documented the unsuccessful search for a treatment for septic shock based on the theory that septic shock is due to endotoxin and its secondarily induced host mediators. These references are available from the author.

Results and conclusion The concept of a shock toxin in trauma and sepsis as promulgated during World War I is correct. This toxin is a thrombogenic aminophospholipid which occurs only on the inner layer of all cell membranes and is liberated by cell destruction. It causes disseminated intravascular coagulation which may obstruct the microcirculation of any or all organs, producing multiple organ failure by microclots. These microclots may be lysed by plasminogen activator and circulation to the organs restored.

Trauma is associated with two types of shock; haemorrhagic or hypovolaemic shock, and shock due to multiple trauma. These types of shock are separate and distinct, although they may occur together, probably in synergy. Haemorrhagic (hypovolaemic) shock is characterized by blood loss (for instance a knife wound to an artery). Traumatic shock is associated with severe tissue damage. Septic shock is associated with infection which may or may not be secondary to trauma. With a tremendous volume of research producing a great volume of data, the syndrome which might be called post-trauma critical illness has greatly complicated the nomenclature. The terms 'bacteraemia', 'septicaemia', 'sepsis syndrome' and 'septic shock' have been used interchangeably. The term 'systemic inflammatory response syndrome' (SIRS) has been added to the term 'sepsis' in an effort to describe the syndrome further.

Trauma and sepsis are the most common causes of death under the age of 45 years. Trauma is the cause of twice as many years of lost potential useful life as either cancer or cardiovascular disease. The treatment of traumatic and septic shock has been very unsatisfactory, the mortality rate remaining at about 50 per cent even though many new treatments have been the object of intense research for many years. Death from septic shock in the USA increased from 35 000 in 1970, to 94 000 in 1980, and to 198 000 in 1990. The death rate from septic shock per 100 000 population increased from 1·7 in 1970, to 4·2 in 1980, 7·9 in 1990, and to 7·9 in 1993[1].

A review of traumatic and septic shock is presented here. It is based on published research papers over the past 120 years including studies in World War I, World War II, the Korean War, the war in Vietnam, and on recent studies in animals and humans in University Medical Centers in El Paso, Washington, DC and Germany. It concludes that the concept of a shock toxin in trauma and sepsis, as promulgated during World War I, is correct. The toxin theory was replaced in the 1930s by the hypovolaemia theory and the endotoxin theory which are shown to be incomplete. A theory of traumatic and septic shock is put forward in this article.

The treatment of haemorrhagic (hypovolaemic) shock is very straightforward and effective, i.e. blood or other fluids delivered intravenously. The treatment of multiple trauma and septic shock is much less satisfactory. Fluid administration helps traumatic and septic shock only as much as hypovolaemia plays a part in the shock. It may play either a very minor role or a great role in either traumatic or septic shock.

Traumatic and septic shock are associated with acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF). This is because both these types of shock are accompanied by disseminated intravascular coagulation (DIC) which may occlude the microcirculation of any or all organs by microclots. ARDS was first shown to be accompanied by DIC and microclots in the Vietnam War in 1964–1972[2–12], when it was called shock lung. What is the cause of the DIC? It has long been held that the DIC of septic shock is caused by endotoxin, a polysaccharide from cell walls of the *Escherichia coli* organism. However, there is another toxin, an autotoxin, which occurs in both traumatic and septic shock and which causes DIC. This toxin is an aminophospholipid that occurs on the inner layer of all cell membranes.

Shock toxin promulgated

In the United States Army Surgeon General's official record of surgery in World War I, shock was equated with wounds and was called wound shock[13]. Shock was said to

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occur 'as a consequence of physical injury, the rupture, tearing or crushing of large amounts of tissue. It is characterized by a low venous pressure, low or falling arterial pressure, rapid thready pulse, diminished blood volume, normal or increased erythrocyte count and hemoglobin percentage in the peripheral blood, leukocytosis, increased blood nitrogen, cold skin moist with sweat, pallid or grayish or slightly cyanotic appearance, thirst, shallow and rapid respiration, often vomiting and restlessness and anxiety changing gradually to mental dullness and lessened sensitivity'[13]. Shock was attributed to a toxic factor arising from damaged and dying tissue[13]. 'There might be no essential difference between the effects of toxin given off by damaged tissue and of toxins resulting from activity of bacteria.' These words were written by the great Walter B. Cannon of Harvard University. However, such a toxic factor has never been found.

Hypovolaemia and endotoxins replace shock toxin

Since the work of Blalock[14], it has been long considered that traumatic shock and haemorrhagic (hypovolaemic) shock are the same. This work was done in the 1920s and does not completely explain traumatic shock. Blalock bluntly traumatized dogs' legs and measured the blood loss in the legs. He concluded that the extravasated blood in the legs could account for the shock produced. However, Hardaway *et al.*[15] have produced fatal traumatic shock in pigs with a normal blood volume. Many patients with traumatic shock die with a normal blood volume. It has been shown that in 'pure' haemorrhagic shock, that is if the blood removed from the animal is treated carefully and not allowed to touch air, glass or anything except a plastic surface, the shock is always reversible by retransfusion[16]. If there is any haemolysis then irreversible haemorrhagic shock results.

For many years, up until World War II, shock and haemorrhage were considered to be separate entities[17]. This played a great part in the emphasis placed on plasma in early World War II because it was thought that in wound shock the haematocrit was high[17]. However, it is now known that hypovolaemic and traumatic shock are both varieties of shock but different and separate, although frequently they occur together[18,19]. This opinion has been expressed by Trunkey[18] and described by Hardaway[19]. Hypovolaemic shock responds well to fluids. Multiple trauma and septic shock respond poorly to fluids. This is because multiple trauma and sepsis are both associated with DIC. Traumatic shock and septic shock are the most common causes of MOF including ARDS. The treatment of hypovolaemic (haemorrhagic) shock is very satisfactory, namely intravenous administration of fluids. However, the treatment of traumatic and septic shock, especially ARDS, has remained unsatisfactory. Of course, respiratory support, metabolic support with fluids and electrolytes, antibiotics and nutritional support are all essential and usually used, but the mortality rate from traumatic and septic shock remains high at 50 per cent or more[20].

Unsuccessful search for treatment of septic shock

Many methods have been used to treat ARDS, originally called shock lung[21–99]. External oxygenation using extracorporeal membrane oxygenators has been helpful, particularly with infants, but less so in adults[19]. Intra-aortic oxygenation has also been useful to a degree but overall the results have not been helpful[19]. Corticosteroids have been tried extensively with generally poor results[19]. Vasoactive drugs, including vasoconstrictors, vasodilators and mixed types, have been of limited use[19]. Endogenous opiates have been employed with mixed results[19]. Many centres have been using monoclonal antibodies to endotoxin with great success in the laboratory[19] and also in some clinical studies[60]. In a Federal Drug Administration-approved multicentre study, many unexpected deaths resulted in the removal from the market of interleukin 1 receptor antagonist[61]. A recent study of monoclonal antibody treatment showed an actual increase in mortality rate associated with canine Gram-negative septic shock[63]. Administration of nitric oxide is under study but so far has not proved effective[20]. Antioxidants, ketoconazole, ibuprofen, indomethacin, sodium nitroprusside, pentoxifylline, antiendotoxin, anticytokine and other agents have not so far proved effective[20]. Recently, an aerosolized surfactant has been advocated for treatment of ARDS but this has not yet affected mortality rates[62].

Despite increasingly complex modes of mechanical ventilation, sophisticated respiratory and haemodynamic monitoring, and a continually expanding array of potent antibiotics, the overall mortality rate has remained constant[20]. Although many drugs have been effective in animals, no effective clinical treatment for multiple trauma shock and septic shock has been found in a review of the recent literature[20]. None of the above drug treatments has been shown to alter the high mortality rate associated with septic shock. Bone, perhaps the foremost authority on sepsis, in a recent article in the *Journal of the American Medical Association*, called for 'rethinking the approach to the complex problem of sepsis because there have been a number of drugs that worked like gangbusters in animal trials, but they have not done anything worthwhile in humans'[96]. Bone in another commentary stated 'Sepsis as a leading cause of death has increased massively just as we were searching for the magic bullet. We must retest our original hypothesis to evaluate its validity. Only by rethinking the assumptions underlying the failed treatments for sepsis can we hope to make strides in saving patients from a sepsis-induced death'[97].

Shaw Warren in the March 1997 issue of the *New England Journal of Medicine* stated 'A remarkable number of clinical trials have been performed in the past decade to evaluate drugs for the treatment of sepsis. The mechanism of action of most of these agents is based on one of two unproved assumptions relating to sepsis in humans. The first is that endotoxin (bacterial lipopolysaccharide) contributes to the morbidity and mortality caused by infection with Gram negative bacteria. The second assumption is that a major part of the pathophysiology in patients with sepsis is due to an over production of one of the many secondarily induced host mediators...Why have all the attempts at treating sepsis failed so far?...In patients with septic shock, blockade of tumour necrosis factor with a fusion protein (a dimeric form of the type II tumor necrosis factor receptor linked with the Fe portion of Ig [immunoglobulin] GI) actually increased mortality'[98]. Baue, also in 1997, stated 'The frequency of infection, sepsis or inflammation in producing MOF led to clinical trials of so called magic bullets for treatment of patients with sepsis. The trials have had either limited success or negative results despite considerable evidence for efficacy or protection by such agents in experimented animals and in studies of normal human volunteers'[99]. Various anti-inflammatory therapies have failed to produce effective results[100,101]. Murine monocolonal antibody to human tumour necrosis factor did not improve survival after septic shock[102]. Therapy against proinflammatory cytokines has not helped[103]. Endotoxin cannot be considered the only mechanism for producing shock[104].

Endotoxin is not alone as a cause of septic shock

For years investigators have focused on the pivotal role of endotoxin, the lipopolysaccharide associated with cell membranes of Gram-negative micro-organisms. It is composed of an *O*-polysaccharide chain, a core sugar and a lipophilic fatty acid. The lipid A portion of the lipopolysaccharide induces expression of cytokine genes through stimulation of receptors on the surface of target cells and activation of the nuclear transcription factor Nf-κ B. This gene activation brings on the inflammatory response and its attendant deleterious effects, i.e. hypotension and organ dysfunction–septic shock. Because it causes a shock-like state when injected into experimental animals, even in nanogram amounts, endotoxin has been implicated as a causative agent in septic shock. However, with our now more detailed understanding of sepsis, it is clear that endotoxin gives rise to a number of inflammatory agents. This may explain why trials in which antiendotoxin antibodies were injected into patients have failed to show consistent benefit. Tumour necrosis factor produced by sepsis is one agent; platelet activating factor, interleukin 1, arachidonic acid metabolites, erythropoietin, endothelin, and interleukins 6 and 8 are also all found in sepsis, and probably play a part in systemic inflammation. Many cytokines and other substances will produce systemic inflammation. Typhoid vaccine was used to cause fever in the 1930s. Endotoxin alone may cause DIC and microvascular obstruction. However, neutrophil–endothelial cell interaction may result in expression of adhesion molecules which may cause endothelial cell damage and increase the permeability of the endothelium. Increased nitric oxide may cause tissue damage by inducing direct oxidant injury.

A shock toxin found (an autotoxin)

All cell membranes (bacterial as well as mammalian) are made up of an inner and an outer layer of phospholipids with thin hydrophilic ends facing inward[64] (*Fig. 1*). It was found that compounds containing choline were distributed through the outer leaflet of the membrane, and that aminophospholipids were found exclusively on the cytoplasmic side of the inner leaflet[65]. It was also established that translocation of the aminophospholipids from the inner to the outer leaflet (as occurs in erythrocytes during 'sickling' and in erythrocytes from patients with paroxysmal nocturnal haemoglobinuria) activates intravascular coagulation[66]. The breaking of the cell wall exposes the inner lining of that wall to the surrounding medium. Trauma breaks red cells. Feola and colleagues[67] found that extremely small amounts of aminophospholipids activate intravascular coagulation, as indicated by a drop in the serum fibrinogen level and deposition of fibrin in the microcirculation of most organs. They also produce thrombocytopenia, leucopenia, fibrinolysis (the appearance of 'fibrin split products' in the plasma), activation of the alternative pathway of complement (increased levels of factors C3q des Arg and C5a des Arg), and possible activation of the kinin system (suggested by the development of circulatory instability and bronchospasm). These aminophospholipids are toxic to the point of being lethal[67]. Aminophospholipids have been infused into rabbits over a 30-min period. The rabbits developed DIC with thrombocytopenia, a low fibrinogen level and the appearance of fibrin split products. The lungs were congested and oedematous, the livers were markedly enlarged and the spleens contained haemorrhagic infarcts.

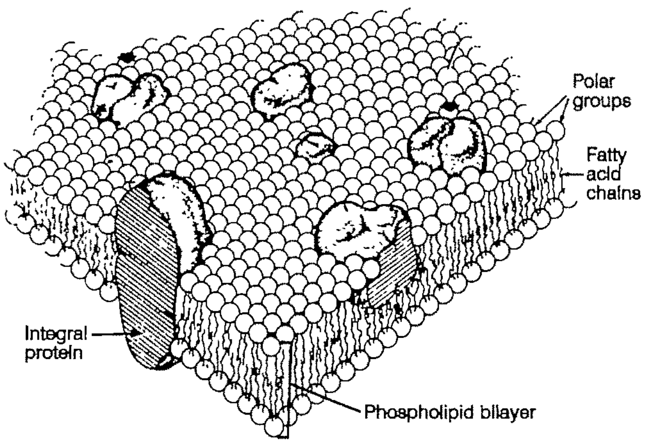

Fig. 1 Basic structure of all cell membranes showing inner and outer surfaces. (Reproduced with permission from the American Association for the Advancement of Science. *Science* 1972; 175: 720–31)

Tuomanen in an article in *Scientific American* tells how her friend, Alexander Tomay, 'accidentally challenged animals with killed pneumococci and yet the animals got sick. Dead bacteria seemed as harmful as living ones. How could this be?'[68]. There are several examples of the toxicity of inner cell walls. The Herxheimer reaction may be due to the broken cell walls of the spirochete. Ascites fluid contains many broken cells and, when reinjected into the circulation by a Leveen shunt, results in DIC. If human amniotic fluid (which contains many broken cells) is injected intravenously into a dog, DIC results[69]. The pulmonary artery pressure rises, blood may become incoagulable and MOF may result[70]. If one filters the amniotic fluid before injecting it, the fluid is harmless[70]. The dead foetus syndrome and the reperfusion syndrome may be due to absorption of damaged cellular debris.

Role of disseminated intravascular coagulation in traumatic and septic shock

DIC was first described by Landois[71] in 1875 when he gave dogs human blood intravenously and found hyalin thrombi in the vessels of the mesentery. In 1951, Schneider noted a decrease in fibrinogen and microscopic fibrin embolism in a patient with placenta abrupto[72]. The first clinical cases of DIC and organ failure were reported in 1954, during the Korean War when Hardaway *et al.*[73] described four patients with acute renal failure after trauma, sepsis or transfusion reaction, all of whom showed decreased or absent fibrinogen levels, a clotting defect and fibrin thrombi. It was postulated that the clotting defect was due to the consumption of clotting factors in an episode of DIC and that renal failure was caused by fibrin microclots in capillaries of the kidney[73]. After experimental work on dogs using administration of human blood, it was shown that DIC could produce acute renal failure[74], haemorrhagic necrosis of the gastrointestinal mucosa[75], liver failure[76,76a], acute pancreatitis[77] and pulmonary failure[78]. In fact, DIC could produce MOF. These syndromes were called 'syndromes of disseminated intravascular coagulation' in an article published in 1961[79] and this was expanded into a book on DIC in 1966[80]. DIC was defined as 'an acute transient coagulation occurring in the flowing blood throughout the vascular tree and which may obstruct the microcirculation. It may or may not result in an accumulation of fibrin but does involve the transformation of fibrinogen into fibrin. It includes the agglutination of platelets and the sticking of leukocytes'.

A clinical study of patients in severe shock, due to trauma or sepsis or both, confirmed DIC in nearly every case[81]. It was noted that trauma to one thigh in pigs produced haemolysis that showed up in the blood beginning about 8 h after trauma and reaching a peak at about 36 h[83,84]. When trauma was combined with haemorrhage it produced a marked change in mortality rate from haemorrhagic shock. If blood was removed from the dog, frozen and thawed (producing haemolysis) and returned to the animal, the mortality rate was zero; if combined with haemorrhage, the mortality rate was high. It was concluded that something in haemolysed blood promoted DIC, but only in the presence of shock (slow capillary flow). Fibrinolysin (plasmin) significantly prevented death, probably by lysing the microclots of DIC[85].

Recent studies have shed new light on traumatic and septic shock

Animal experiments

These experiments were approved by the United States Animal Use Committee. Trauma in pigs (60 blows to both thighs without skin, bone or vessel damage), kept under anaesthesia for 48 h or until death, produced a mortality rate of 100 per cent within 48 h[15] even though blood volume was kept at normal levels. Death was due to significant respiratory failure and significant liver and kidney failure[86]. Some 250 000 units of urokinase diluted in 20 ml saline were injected over a 20-min period starting 20 min after trauma. Death, ARDS and organ failure were completely prevented[15]. Experiments with pigs using commercial polysaccharide endotoxin were then attempted, but required such large doses of endotoxin to cause a death that it was decided to use a killed culture of *E. coli*. A small dose of killed *E. coli* produced death and MOF. Death and MOF were significantly prevented by intravenous administration of 250 000 units of urokinase 20 min after *E. coli* injection[87]. Control pigs' lungs were cyanotic, congested and oedamatous; treated pigs' lungs were aerated and pink. All clotting variables remained within normal parameters except in the single (control) pig which survived 24 h without treatment. Its blood was incoagulable. All treated pigs' clotting parameters remained normal. A similar experiment using killed pneumococci produced similar results.

Human studies

These studies were approved by the Institutional Review Board and the Food and Drug Administration in the USA as a phase I study[88]. The aim of this study was to evaluate the safety of plasminogen activator in lysing the microclots of DIC. Nineteen patients with severe traumatic or septic shock were studied. All developed MOF with severe ARDS. In accordance with restrictions imposed by the Food and Drug Administration, treatment with plasminogen activator could not be started until at least 48 h after surgery or trauma and until respiratory therapy with oxygen and positive end expiratory pressure had failed for 24 h to raise the arterial partial pressure of oxygen (P_{aO_2}) to 60 mmHg[89]. Clotting variables had to be normal for the patient to enter the protocol. The dosage of urokinase was 2200 units per kg body-weight as a bolus in 10 min, followed by 2200 units per kg body-weight per h for 24 h. These patients were all *in extremis* yet all but one responded to plasminogen activator therapy with a marked and sustained rise in P_{aO_2} (*Figs* 2 and 3). None bled or had any change in clotting variables.

A case of severe DIC was recently reported[105,106]; a 4-month-old infant was comatose, had a severe purpuric rash, splenomegaly and a partial thromboplastin time over 100 s. He was given hydrocortisone, dopamine and adrenaline without benefit; prognosis was poor. With written consent, tissue plasminogen activator (tPA) was infused at a rate of 0·05 mg/kg for 1 h and 0·025 mg/kg for a further 3 h. During the 4-h infusion, blood pressure increased markedly. His extremities became warm and pulses became palpable. Urine output increased to 1 ml per kg per h. Several blackish areas of skin became pinker and remained viable. It was stated 'We have described a

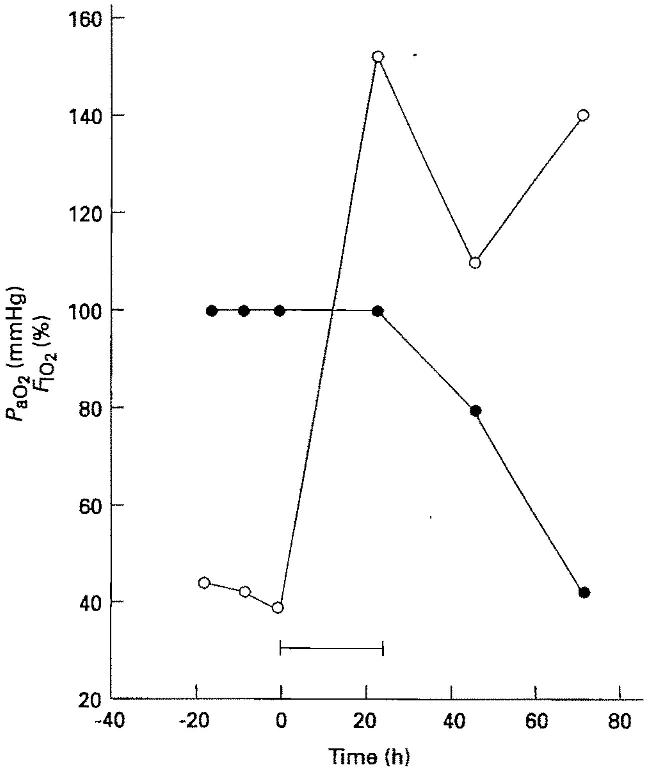

Fig. 2 Arterial partial pressure of oxygen (P_{aO_2}, ○) and fraction inspired oxygen (F_{IO_2}, ●) in a patient with septic shock; after treatment with oxygen, a respirator and positive end expired pressure, the P_{aO_2} was only 39 mmHg. After a course of plasminogen activator (———), it rose to 150 mmHg. F_{IO_2} could then be lowered and P_{aO_2} remained raised. The patient went to recovery. No clotting variables changed. (Reproduced with permission from Health Communications, Inc., Metuchen, New Jersey, USA. *Advances in Therapy* 1994; 11: 43–51)

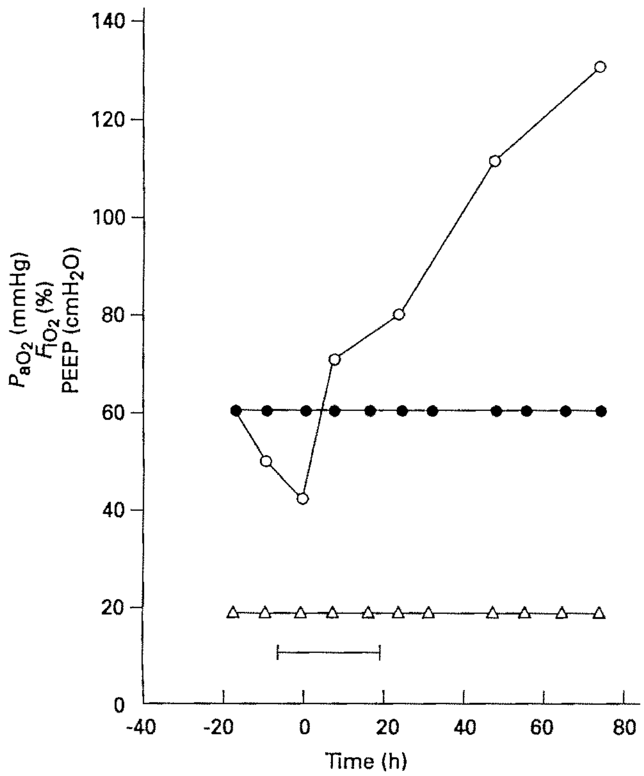

Fig. 3 Arterial partial pressure of oxygen (P_{aO_2}, ○), fraction inspired oxygen (F_{IO_2}, ●) and positive end expired pressure (PEEP, △) in a patient with traumatic shock. P_{aO_2} had fallen to 40 mmHg under 60 per cent oxygen and PEEP. After urokinase (|——|), P_{aO_2} rose to 130 mmHg, and F_{IO_2} and PEEP remained constant (Reproduced with permission from Health Communications, Inc., Metuchen, New Jersey, USA. *Advances in Therapy* 1994; *11*: 43–51)

case of potentially fatal meningococcal purpura fulminans in an infant who did not respond to aggressive conventional therapy and in whom tPA infusion appeared to re-establish major organ perfusion and reverse cardiovascular collapse, resulting in survival'.

The diagnosis of DIC is often thought to be associated with a bleeding tendency, especially afibrinogenaemia. In reality afibrinogenaemia is rare; most patients with DIC actually have a high fibrinogen level[91] because of the very rapid rate of fibrinogen manufactured by the liver under the stimulation of stress[92]. Bleeding in DIC when it does occur is usually due to depletion of other coagulation factors[91]. The appearance of fibrinolysis is a protective response of the body to try to dissolve the microclots of DIC[73]. DIC in experimental animals produced by trauma or sepsis does not cause a rise in prothrombin time or partial thromboplastin time[85] and its diagnosis can only be made by raised levels of fibrin split products[80]. It has been established that only the more severe cases of DIC may develop a clotting defect; chronic and mild DIC does not alter the clotting mechanism[107]. The treatment of DIC by fibrinolytic enzymes is not new and was first carried out in dogs in 1963[85,93,94]. The use of fibrinolysin or plasminogen activators has never caused bleeding either in the treatment of animals or humans[89,90,95,96]. In fact, plasminogen activation should prevent the incoagulability produced by DIC.

Administration of a plasminogen activator immediately after trauma would seem to be dangerous. However, it did not cause any bleeding in the pig model. I believe the reason for this is that blood outside the vascular tree has already clotted and is not in contact with plasminogen activator, whereas blood in the vascular tree is subject to action by plasminogen activator and circulation is restored.

Conclusion

A theory of traumatic and septic shock is presented. It postulates that both traumatic and septic shock are accompanied by DIC, which temporarily occludes the microcirculation of any or all organs, temporarily cutting off the circulation to those organs and causing MOF. DIC may be brought on by rupture of the walls of red cells, tissue cells, bacteria, or all three. Red cells and tissue cells may be broken by trauma, cold or heat, anoxia, viruses or plasmodia. Bacterial cell walls may be broken by antibiotics, heat or antibodies. The inner layer of all cell walls consists of thrombogenic aminophospholipids. When cells are broken, this thrombogenic phospholipid may initiate DIC, acting as an autotoxin. DIC may block the microcirculation of any or all organs, causing ARDS and MOF. It is postulated that the polysaccharide endotoxin is not the main initiator of septic shock, but that thrombogenic phospholipids are. Microclots of DIC in an organ's microcirculation may be lysed by a plasminogen activator. Lysing of microclots in the lung restores the microcirculation in that organ and effectively treats DIC. Bleeding has not been caused in the dosage described. The administration of urokinase for the treatment of traumatic or septic shock in pigs is both safe and effective. Its administration for the treatment of septic or traumatic shock in humans has proved safe in a phase I study. The effectiveness of this agent in the treatment of septic shock or traumatic shock must await a prospective randomized study, which is already under way in 20 centres.

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Digest

Der Chirurg

For this quarter's digest, Professor Christian Herfarth and Dr Thomas Lehnert have selected the best from the January to March 1998 issues of *Der Chirurg*. A digest for the BJS for the same period, written by Mr Colin Johnson, appears in the German journal.

The new year's reviews opened with a series on vascular surgery with a special emphasis on vascular surgical techniques in abdominal surgery[1–3]. The February and March reviews addressed open and laparoscopic antireflux surgery of the oesophagus[4–7] and the influence of *Helicobacter* infection on the development of ulcer disease[8], gastric lymphoma[9] and carcinoma[10].

Postcholecystectomy syndrome

Cholecystectomy is one of the most frequently performed operations in visceral surgery. Since the operation is usually performed in an elective situation to cure long-standing, although hardly ever life-threatening, symptoms of cholecystolithiasis, the patient understandably expects the complete absence of symptoms after operation. Complaints following cholecystectomy have been summarized as 'postcholecystectomy syndrome'. Surgeons from Basel[11] have examined the prevalence of symptoms more than 1 year after laparoscopic cholecystectomy. Between September 1994 and August 1995 a total of 268 consecutive patients undergoing elective laparoscopic cholecystectomy was studied prospectively. Patients undergoing primary conventional cholecystectomy were excluded, as were those requiring conversion to open cholecystectomy. Of 268 patients initially entered into the trial, 253 patients could be evaluated at least 12 (median 16 (range 12–25)) months after operation. Typical preoperative complaints, defined as right upper quadrant pain lasting for more than 60 min, were recorded in 59 per cent of patients ($n = 149$). Some 128 patients had undergone previous laparotomy for other diseases.

Postoperative complaints were classified according to Visick. At 1 year after laparoscopic cholecystectomy only 65 per cent of the patients ($n = 164$) were completely free of symptoms (corresponding to Visick grade I). Seventy-two patients were Visick II, and Visick grades III and IV were recorded in 17 patients. In 22 patients a cause for the symptoms could be determined (residual calculi, three; biliary peritonitis, one; subhepatic abscess, one; incisional hernia, one; scar-related pain, six; reflux or peptic ulcer disease, ten). No cause could be detected in 67 patients and their symptoms were considered to be functional in origin. No correlation was observed between the type of preoperative symptoms (typical *versus* atypical) or the type and number of previous laparotomies and the presence or absence of postoperative symptoms 1 year after laparoscopic cholecystectomy.

Neural networks

Predicting the outcome of disease has been at the centre of medical interest since the time of Hippocrates. In modern medicine this question is particularly relevant in the intensive care of patients with septic shock. To date scoring systems aiming to predict final outcome of such patients are largely too inaccurate to justify their use in clinical decision-making. A group from Frankfurt[12] has accepted this challenge and adopted a new statistical approach to the problem. The neural network concept was applied to 114 patients with a diagnosis of septic shock who were treated between November 1993 and October 1995. Septic shock was defined as sepsis with hypotension despite adequate fluid replacement together with perfusion defects, lactate acidosis, oliguria or acute mental changes, and which required the use of inotropic or vasopressive substances to correct hypotension. Overall in this group 54 patients (47 per cent) died. The Acute Physiology And Chronic Health Evaluation (APACHE) II score was similar for survivors (24 patients) and non-survivors (26). The following clinical data from these patients were entered into the network during the training phase including 91 patients: sex, age, respiratory frequency, fraction of inspired oxygen, partial pressure of oxygen and carbon dioxide, pH, maximum ventilation pressure, white cell count, thromboplastin time, thrombocytes, antithrombin III, lactate, creatinine, heart rate, systolic blood pressure, body temperature, and requirement for dopamine, dobutamine and sodium bicarbonate. After training the network and including parameter changes observed between days 1 and 2 of the intensive care stay, the data sets from the remaining 23 patients were used for actual testing of the neural system. The network subsequently predicted fatal outcome correctly in all ten patients who died. Survival was predicted correctly in 12 of 13 patients to give a sensitivity of 100 per cent and a specificity of 92 per cent. The authors conclude that the neural network could prove useful for identification of patients who require maximum effort to prevent death, but at the same time they realize the danger of the neural network fatalistically being considered a doom machine.

Postoperative alcohol withdrawal

Alcohol consumption, make no mistake, is a major pastime in Europe to an extent that sudden interruption of alcohol intake for prolonged periods may result in life-threatening metabolic disturbance. In surgery this severe complication may be anticipated in patients undergoing major operative procedures for conditions specifically associated with sometimes excessive alcohol intake, such as cancer of the oesophagus or chronic pancreatitis. To adjust to the specific postoperative needs of such patients, preoperative information about the potential risk of alcohol withdrawal syndrome would be desirable. However, experience has shown that history-taking is notoriously unreliable regarding alcohol consumption. This may be due to poor recall by the patient or to a mutual misunderstanding between doctor and patient, for instance in wine-growing areas drinking a bottle of wine per day may not be considered as 'consuming alcohol' by many. An objective, simple and reliable marker of alcohol abuse would be highly desirable to improve preoperative risk assessment.

Hölscher and associates[13] have undertaken a prospective study of the value of preoperative determinations of carbohydrate-deficient transferrin (CDT) for prediction of the postoperative course. CDT results from inhibition by acetaldehyde of the glycosylation of transferrin. After an alcohol intake of 50–80 g per day for 1 week, CDT concentration increases. The half-life of this increase is 12–17 days. The study was performed in 46 consecutive patients with squamous cell carcinoma of the oesophagus scheduled for oesophageal resection between June 1994 and January 1996. For the purpose of the study alcohol consumption of less than 75 g/day was considered normal, that of 75–150 g/day as increased and that of more than 150 g/day as excessive. Logistic regression analysis determined alcohol consumption and increased CDT levels as independent predictors of postoperative complications and withdrawal symptoms. However, the sensitivity and specificity regarding postoperative withdrawal symptoms were only 71 and 84 per cent respectively.

Gastric banding

Morbid obesity is not very common in Germany and so gastric banding is performed infrequently. While the editors of this digest have seen the occasional individual obviously suffering from morbid obesity, they have not been called upon to treat such patients surgically. Still, as it is estimated that obesity-related disorders cost healthcare providers each year the same amount that is spent on malignant diseases, the need for effective treatment is evident.

Only a few centres in Germany are likely to be exposed to sufficient numbers of patients with morbid obesity to develop experience with the laparoscopic treatment of this condition. Kunath and co-workers[14] from Berlin are among them. Between August 1994 and July 1997 they saw 873 patients with morbid obesity and offered laparoscopic surgical treatment to 224. Operative treatment was indicated for patients with a body mass index (BMI) greater than 30 kg/m^2 or a BMI greater than 25 kg/m^2 associated with psychosocial disturbance. Contraindications were alcohol or drug abuse, overt lack of self-discipline and chronic medication with corticosteroids or salicylates. The authors used a laparoscopic technique of gastric banding via five incisions. The use of a gastrotonometer to adjust the gastric band has been abandoned, because it was considered that intraoperative adjustment might cause gastric wall oedema. The band's cuff was therefore adjusted after 4–6 weeks to allow formation of the gastric pouch. Mean(s.d.) age of the patients was 41(9) years and BMI was 45(5) kg/m^2. Five operations had to be converted to the open operation and in a further five patients the band could not be placed. Gastric pouch volume was adjusted to 20 ml during operation.

The authors now report the results in 208 patients in terms of weight reduction achieved and late technical complications. Pouch dilatation was recorded in 11 patients and slipping of the gastric band in six. Four patients had perforation or penetration of the gastric wall. Port-related complications, such as infection or port migration, were observed in 21 patients. A total of 43, mostly minor, complications was observed in 20 per cent of 208 patients followed. Absolute weight loss in 180 patients followed for more than 3 months was 14 kg after 3 months and 28 kg after 24 months. Relative loss of excessive weight was 25 per cent at 3 months and 50 per cent at 24 months. The authors stress that successful treatment requires careful selection of patients likely to benefit from the procedure. Patients with excess food intake due to a lack of satiety and a long history of failed dietary treatment, often as inpatients, were the best candidates. They also emphasize that gastric banding preserves the stomach and is potentially reversible. The procedure is burdened with a number of technical slips and the authors recommend that at least 50 operations should be performed by each surgeon per year, although in their own experience, with seven surgeons performing the operation, only three of them have performed more than 50 operations during the 3-year observation period.

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SURGERY TODAY
The Japanese Journal of Surgery

Digest

Professor Keizo Sugimachi, Editor-in-Chief of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the January to March 1998 issues of his journal for this quarter's digest. A digest of *BJS* for the same period written by Mr Colin Johnson, European Editor, appears in the Japanese journal.

Oesophagus

The first paper was designed to clarify the clinical and pathological features of diffusely infiltrative squamous cell carcinoma of the oesophagus[1]. Diffusely infiltrative squamous cell carcinomas were classified grossly into two types: scirrhous carcinoma ($n=7$) and non-scirrhous carcinoma ($n=3$). Scirrhous-type carcinoma was associated with a prominently thickened oesophageal wall with strictures, whereas the non-scirrhous type demonstrated thickening of the oesophageal wall with no strictures. Microscopically, all patients had lymph node metastases and lymphatic invasion. Blood vessel invasion was found in seven patients and extranodal invasion in seven. The prognosis of patients with both types of carcinoma was extremely poor. Only two patients who underwent curative surgery as well as chemoradiotherapy survived for more than 1 year. The authors believe that further morphological studies on the early stages of diffusely infiltrating oesophageal carcinoma should be performed. New treatment strategies such as intensive preoperative chemoradiotherapy based on sensitivity testing of individual patients may be of value in treating the advanced stages of this disease.

Patients who have undergone major surgery such as oesophagectomy may develop peripheral oedema in the immediate postoperative period, the cause of which is not fully understood[2]. The purpose of this study was to determine the mechanism of this phenomenon. Finger oedema was measured as a marker for peripheral oedema before and after oesophagectomy in eight patients. Plasma interleukin (IL) 6 concentration was also measured by an enzyme-linked immunosorbent assay. Finger oedema increased markedly in the immediate postoperative period and remained significantly raised until after the third postoperative day compared with the preoperative value ($P<0{\cdot}05$). Plasma IL-6 levels were also markedly increased in the immediate postoperative period and remained significantly raised on the second postoperative day compared with the preoperative value ($P<0{\cdot}05$). The degree of finger oedema correlated strongly with the plasma level of IL-6 ($r=0{\cdot}71$, $P=0{\cdot}001$). These findings indicate that peripheral oedema after oesophagectomy may be caused by a proinflammatory cytokine response.

Stomach

It is well known that surgical intervention on the stomach greatly alters gastric function and gastric emptying. Imada *et al.*[3] evaluated the difference in postoperative gastric remnant emptying following pylorus-preserving gastrectomy (PPG) and conventional subtotal distal gastrectomy (CDG) using sulphamethizole capsule food. The subjects comprised 18 patients who underwent PPG and 23 who had CDG for early gastric carcinoma. While delayed gastric emptying was observed early after PPG, 1 year after PPG it was markedly accelerated compared with that in the early postoperative period. However, delayed emptying was slower than that in patients who had CDG. On the other hand, rapid gastric emptying was observed early after CDG and did not change with time. These findings suggest that, although PPG results in stasis in the early postoperative period, it seems later to prevent unduly rapid emptying.

Serum levels of pepsinogen A were measured in patients who underwent various forms of gastric resection to assess the influence of *Helicobacter pylori* colonization[4]. Included in this study were 48 patients who underwent subtotal gastrectomy for peptic ulcer, 36 who had radical subtotal gastrectomy for gastric carcinoma, 16 who had truncal vagotomy plus antrectomy, 24 with recurrent ulcer and 27 who underwent total gastrectomy. Mean(s.d.) serum pepsinogen A levels in these five groups and in 40 healthy controls were 49·1(30·4), 30·0(14·8), 44·8(21·7), 66·4(42·8), 8·7(3·0) and 94·7(27·9) ng/ml respectively. All patients except those with recurrent ulcer showed a diminished pepsinogen A level. The *H. pylori* colonization rate of patients who underwent partial resection was 46, 22, 50 and 54 per cent respectively ($P<0{\cdot}05$). Age, sex, smoking, type of gastroenterostomy and underlying disease did not have any influence on the measured pepsinogen A levels. However, a higher pepsinogen A level was observed in patients colonized with *H. pylori* who underwent subtotal gastrectomy for peptic ulceration or who had recurrent ulcer. The authors conclude that various forms of distal gastrectomy, but not recurrent ulceration, elicit an indistinguishable acid secretory ability whereas *H. pylori* colonization is responsible for the higher serum pepsinogen A levels in some patients following surgery for peptic ulcer.

Colon

The authors investigated the occurrence of apoptotic cell death in 104 colorectal carcinomas by terminal-deoxynucleotidyl transferase-mediated 2′-deoxyuridine 5′-triphosphate–diotin nick end-labelling (TUNEL) to determine whether apoptosis might be a useful prognostic factor[5]. The apoptotic index (AI) was calculated as the percentage of positive cancer cells per 1000 cancer cells; median AI was 4·1 (range 1·9–4·7). Apoptosis was observed less frequently in tumours with higher malignant potential, such as those at advanced stages (Dukes B, C and 'D') than in those at Dukes stage A ($P<0{\cdot}05$); in tumours showing evidence of moderate differentiation than in well-differentiated lesions ($P<0{\cdot}05$); and in tumours with venous invasion or lymph node metastasis than in those without these features ($P<0{\cdot}05$). Moreover, the subgroup of patients with a low AI of less than 4·1 had a significantly lower survival rate than the subgroup with a high AI in Dukes C tumours, the 5-year survival rate being 33 *versus* 68 per cent ($P<0{\cdot}05$, Cox–Mantel test). The findings suggest that less apoptosis might result in a greater progression of colorectal carcinoma, and that the rate of apoptosis might be an indicator of the degree of malignancy. Thus it would appear that the frequency of apoptosis in tumour cells could be a useful prognostic factor in patients with colorectal carcinoma.

The serum levels of intercellular adhesion molecule (sICAM) 1 and of endothelial leucocyte adhesion molecule (sELAM) 1 were determined in 40 patients with colorectal cancer[6]. sICAM-1 and sELAM-1 levels in the drainage venous blood adjacent to a tumour correlated significantly with those in the peripheral venous blood in patients without evident haematogenous dissemination of tumour cells. The sICAM-1 level in peripheral venous blood was significantly higher in patients with hepatic metastases, whereas sELAM-1 concentration was significantly higher in those with pulmonary metastases. An immunohistochemical study of metastatic sites in the liver revealed that ICAM-1 was expressed in cancer stroma but not in the cancer cells. In conclusion, sICAM-1 and sELAM-1 levels in the peripheral venous blood in patients with colorectal cancer without any distant metastasis are likely to reflect the topical production of these cell adhesion molecules and appear to be instructive in predicting haematogenous dissemination in patients with colorectal cancer.

Vascular surgery

Ohta *et al.*[7] studied the incidence of limb salvage and patient survival rates among elderly patients with advanced leg ischaemia. They reviewed the records of 159 patients treated for advanced ischaemia over a 15-year period at Aichi Medical University, of whom 74 were aged over 75 years and 85 were between 65 and 74 years. There was a collective total of 186 limbs, 82 in the older group and 104 in the younger patients. The older group had a greater proportion of women and a higher incidence of coronary heart disease, pulmonary dysfunction and acute onset of advanced ischaemia than the younger group. Limb salvage was achieved in 73 per cent of affected limbs in the older patients and in 92 per cent of limbs in the younger group. The poor limb salvage rate in the older group was related mainly to the high initial amputation rate. Timely revascularization should be attempted whenever possible, and should not be abandoned simply because the patient is deemed too old. The 1-, 3- and 5-year survival rates in the older group were 59, 28 and 23 per cent respectively, markedly poorer than the expected survival rates of an age- and sex-matched Japanese population at 1, 3 and 5 years, which are 93, 79 and 65 per cent respectively. Thus, advanced limb ischaemia carries a poor prognosis to the point of being life-threatening, and further continuous systemic management with the collaboration of physicians and surgeons must be provided even after the patient has left hospital.

To compare the surgical results of patients with ruptured and non-ruptured abdominal aortic aneurysm (AAA), 267 consecutive patients treated surgically for AAAs were reviewed[8]. Patient characteristics, pre-existent risk factors, perioperative factors, and postoperative early and long-term survival rates were compared between patients in the ruptured aneurysm group ($n = 27$) and those in the non-ruptured aneurysm group ($n = 240$). Multivariate analysis to predict postoperative survival was also conducted in the group of patients with ruptured aneurysm. The hospital mortality rate was 3·4 per cent (eight of 232) for patients with no rupture and 22 per cent (six of 27) for those with a ruptured aneurysm ($P < 0.001$). The maximum size of the aneurysm, period of preoperative hypotension and intraoperative bleeding volume were significantly greater in patients with a ruptured aneurysm than in those with no rupture. The 5- and 10-year cumulative survival rates in the group with rupture were 88·1 and 42·0 per cent, comparable to those in the group with no rupture. The incremental risk factors for hospital death in patients with ruptured AAA included advanced age, preoperative hypotension (less than 80 mmHg) and postoperative renal failure requiring dialysis. These findings show that the interval from rupture to cross-clamping must be shortened, maintaining haemodynamic stability to avoid prolonged hypotension. Reducing risk factors and minimizing deterioration of organ functions after operation would be essential to improve the prognosis of patients with ruptured AAA.

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Cystic tumours of the pancreas

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Background Cystic pancreatic tumours may be misdiagnosed as pseudocysts.

Methods From August 1990 to January 1998, 21 patients (16 women) with a median age of 60 years underwent operation for a cystic mass in the pancreas with histological confirmation of neoplasia (six serous cystadenoma (SCA), three mucinous cystic adenoma (MCA), ten mucinous cystadenocarcinoma (MCAC), one ductal adenocarcinoma with cystic degeneration, one cystic islet cell tumour).

Results While the lesion had been labelled as a pseudocyst in eight patients, only one patient (MCA in the pancreatic head) had had acute pancreatitis previously. In seven patients the computed tomogram (CT) lacked suspicious neoplastic features, while endoscopic retrograde cholangiopancreatography, angiography and percutaneous cyst fluid analysis were unhelpful or misleading in 16 of 18 investigations with respect to differentiating tumour from pseudocyst. Attempted operation for cure was performed in 18 patients despite diagnostic delays of up to 6 years and initial treatment with cystenterostomy in two cases.

Conclusion Retrospective review revealed that all 21 cystic neoplasms could be diagnosed before operation by a history excluding previous pancreatitis (20 of 21 patients) or a CT suspicious for neoplasia (14 of 21). The diagnosis relies more on absence of previous pancreatitis and a suspicious clinician who errs on the side of resecting a pseudocyst rather than watching or draining a cystic neoplasm.

The most clinically significant feature of cystic neoplasms is their ability to masquerade as a pseudocyst, which delays correct management and can affect survival[1–4]. Furthermore, current imaging modalities may not be sufficiently specific to differentiate the two[5,6]. The authors' recent experience of these tumours was reviewed to highlight the diagnostic and management problems associated with cystic masses in the pancreas.

Patients and methods

Retrospective review of discharge summaries and operation records revealed 24 patients who had undergone surgery for a presumed cystic neoplasm of the pancreas at the Royal Infirmary of Edinburgh between August 1990 and January 1998. All radiological findings were reviewed retrospectively without patient history by an experienced radiologist with a specialty pancreatic interest (D.R.). Histopathology specimens were reviewed independently by a single pathologist.

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Results

Twenty-one patients (16 women) of median age 60 years underwent surgery for a cystic mass in the pancreas. There were no cases of mucinous ductal ectasia or papillary cystic tumour (*Table 1*). Over the 7-year period a further three patients (not included in this review) underwent distal pancreatectomy and splenectomy for a presumed cystic tumour found on histological examination to be a benign pseudocyst.

Presenting features

Pain had been present in 16 patients (and radiated to the back in ten) for a median of 13 (range 2–72) months before operation. Weight loss of more than 5 kg occurred in ten patients. Risk factors for pancreatitis included

Table 1 Clinical features of cystic tumours of the pancreas

Histological diagnosis	No. of patients	Sex ratio (M:F)	Medican (range) age (years)	Location		Tumour size (cm)
				Head	Body-tail	
Serous cystadenoma	6	0:6	68 (52–77)	1	5	8 (5–13)
Mucinous cystadenoma	3	0:3	30 (28–45)	1	2	11 (3–15)
Mucinous cystadenocarcinoma	9	3:6	65 (22–82)	3	6	7 (3–10)
Ductal adenocarcinoma (cystic degeneration)	1	1:0	68	0	1	8
Cystic islet cell tumour	1	1:0	55	1	0	6
Total	21	5:16	60 (22–82)	6	14	8 (3–15)

alcohol consumption greater than 100 g per week (three patients), known gallstones or previous cholecystectomy (two) or both (five). A documented attack of acute pancreatitis thought to have been associated with a pseudocyst occurred in a 34-year-old woman with a mucinous cystic adenoma (MCA) in the head of the pancreas. There were two diabetic patients. Three patients were asymptomatic and the lesions were discovered incidentally. An erroneous diagnosis of pseudocyst had been made in eight patients at some stage before operation. A palpable abdominal mass was present in six patients. Two of the three patients with masses in the pancreatic head were clinically jaundiced. Raised serum amylase levels were noted in six patients (two with MCA, four with mucinous cystadenocarcinoma (MCAC)), with a median level of 450 (range 383–1877, normal range 80–300) units/l recorded before operation, endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous biopsy.

Radiology

Review of ultrasonograms and computed tomography (CT) images confirmed a cystic mass in all patients, but a neoplasm was misdiagnosed as a benign pseudocyst in seven of 21 cases. In none of these seven cases were there radiological features suggestive of neoplasia rather than pseudocyst. Only one of the six patients with serous cystadenoma (SCA) had multiple cysts on CT revealing the characteristic features of central calcification with a sunburst appearance. Of the other five patients with SCA, four had appearances on CT suspicious of a cystic tumour, being due to the presence of mural nodules in two, a lobulated appearance and cyst wall thickness of 4 mm in one and a septum in the other. Of 13 mucinous cystic neoplasms (MCNs), four revealed multilocularity, four cyst wall calcification, five mural nodules and one septa. The five patients with MCN erroneously diagnosed on radiology as a pseudocyst had CT appearances of a solitary pancreatic cyst associated with features of chronic pancreatitis in three patients (pancreatic atrophy with pancreatic calcification) or splenic infarction in two. The single patient with cystic degeneration of a ductal adenocarcinoma had an 8-cm unilocular cyst in the body of the gland without features on CT to suggest neoplasia other than a wall thickness of 4 mm.

In the seven patients in whom ERCP was undertaken, the examination revealed extrinsic compression of the pancreatic duct in four and extravasation of contrast into the lesion in two (MCN, one; MCAC, one). Angiography revealed displacement of vessels about the cystic mass in all six studies. The mass was avascular in four cases and consistent with a hypervascular neoplasm in two (one with SCA, one with cystic islet cell tumour). Of five percutaneous needle aspirations in four patients with MCAC and in one with SCA, one aspiration revealed malignant cells, four were acellular and one had a raised cyst amylase level greater than 100 000 units/l without a previous documented episode of acute pancreatitis (MCAC).

Procedure and outcome

An attempted curative resection was performed in 18 of 21 patients (Whipple resection, four; distal pancreatectomy and splenectomy, 14); 17 patients were alive and well a median of 50 (range 4–96) months after operation with no signs of recurrence. Three patients underwent palliative procedures due to the presence of local invasion. One patient with cystic degeneration of an adenocarcinoma died 6 months after operation and both patients with irresectable MCAC are alive 12 and 66 months after gastrojejunostomy. All 21 operative procedures were performed without significant morbidity and no postoperative death.

Ten patients had had symptoms for more than 12 months and two had cystenterostomy performed before referral. One 30-year-old woman underwent cystogastrostomy with biopsy of the cyst wall, which on histopathology confirmed MCN. Some 2 months later a distal pancreatectomy with splenectomy was performed with no signs of recurrence at 49 months. The second patient was a 76-year-old man who underwent an open 'pseudocyst' drainage procedure in 1985 followed by a cystogastrostomy in 1991 for recurrence. While frozen-section examination of the cyst wall was normal, the formal report confirmed an epithelial lining in the cyst wall. Failure of cyst resolution 20 months later led to distal pancreatic resection confirming MCAC with involved resection margins. The patient died 35 months later from tumour recurrence.

Discussion

The experience from this series of patients supports the view that cystic neoplasms of the pancreas are underdiagnosed and frequently mismanaged as a pseudocyst[1–6]. By 1985, Warshaw and colleagues found that 37 per cent of pancreatic cystic tumours were assigned a diagnosis of pseudocyst before definitive diagnosis[7], but with increasing experience an erroneous diagnosis rate of only 9 per cent was achieved in the same institution 10 years later[1].

The most reliable points on history in the present series were the absence of a previous attack of pancreatitis, often associated with a negative history of gallstones or alcohol abuse. Although CT reliably detects a cystic mass, features suggestive of neoplasia, such as cyst wall thickness, calcification, mural nodules, multiple locules or septa, may be lacking[8,9]. ERCP may detect a communication with the ductal system in up to 65 per cent of pancreatic pseudocysts[8], but this occurred in two of seven patients with MCNs, none of which was considered histopathologically to represent mucinous ductal ectasia (intraduct papillary neoplasia). Others[1,4] have reported similar findings in 22 per cent of cases. Angiography may occasionally reveal a hypervascular tumour, but the more common finding is a hypovascular mass, entirely consistent with a pseudocyst[1,10].

Percutaneous needle aspiration of cyst fluid has been reported to help differentiate pseudocysts from cystic neoplasms. Lewandrowski *et al.*[11] analysed fluid from 26 pancreatic cysts (nine pseudocysts, 17 cystic neoplasms) and revealed that high levels of the tumour markers carcinoembryonic antigen and CA-125 or a high viscosity were suggestive of cystic neoplasia, with amylase levels a poor discriminator of cysts. Cytology was helpful only in mucinous tumours. with eight of nine MCNs showing epithelial cells and two of four MCACs containing malignant cells[11]. Hammel and colleagues[12] noted that a cyst amylase level greater than 5000 units/ml was only 74 per cent specific in distinguishing pseudocysts from neoplastic cysts. Some workers have found that cyst fluid tissue polypeptide antigen and CA-72.4 levels are more likely to be raised in mucinous cystic tumours, particularly

MCACs[13,14]. These tests are useful to help support a diagnosis of neoplasia; however, a negative result does not imply a pseudocyst. Similarly there remains the concern of the risk of seeding viable malignant cells into the peritoneum or along the needle tract, as has been well documented in ductal adenocarcinoma of the pancreas.

Intraoperative differentiation of pancreatic cysts is difficult[1,3,5,7]. While cystic tumours are often discrete with a normal surrounding pancreas, pseudocysts appear to have a thicker wall adherent to omentum or stomach, but this is not a uniform finding[1]: six of 21 patients in the present series had a wall thickness greater than 4 mm. Frozen-section histopathology of cystic neoplasms may be normal, as shown in one patient with MCAC in the present series. Even generous biopsies may be misleading as the epithelial lining is incomplete in 40 per cent of mucinous cystic tumours[15] with denuded areas comprising up to 98 per cent of the wall[1]. Intraoperative ultrasonography can help differentiate pseudocysts from cystic neoplasms; however, inflammatory material within a pseudocyst may resemble the features of a neoplasm[3].

Despite the wealth of 'invasive' testing of pancreatic cysts (ERCP, angiography, percutaneous sampling), a simple history excluding previous pancreatitis or CT images suspicious for neoplasia would have led to a correct diagnosis in 21 patients in the present series. Pseudocysts are approximately ten times more common than cystic neoplasms in the pancreas[16] and, since radiology[8,9], cyst fluid analysis[11,13,14,17] and even operative differentiation[1] with frozen section cannot always be absolute in discriminating between the two, the only sure way of excluding a cystic tumour may be radical excision. Such an approach can be supported only when the morbidity of such surgery is minimal.

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Sodium fusidate and the cytokine response in an experimental model of acute pancreatitis

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Background New therapies designed to downregulate the aberrant immune response associated with severe acute necrotizing pancreatitis (ANP) are being increasingly investigated in different experimental models of ANP. The aim of this study was to test the potential effects of sodium fusidate on the course of severe ANP in rabbits.

Methods ANP was induced in 20 rabbits by retrograde injection of 5 per cent chenodeoxycholic acid into the pancreatic duct followed by duct ligation. The rabbits were allocated to pretreatment with intravenous physiological saline or sodium fusidate 80 mg/kg 30 min before the induction of ANP. Levels of serum amylase, lipase, tumour necrosis factor (TNF) α, interleukin (IL) 8, glucose and calcium, and leucocyte count were measured every 3 h for a total of 12 h. At the end of the experiment, ascitic fluid was collected and the pancreatic, lung and kidney tissues were obtained for histological examination.

Results Pretreatment with sodium fusidate reduced the mortality rate from six of ten to three of ten ($P < 0{\cdot}05$) and reduced the output of ascitic fluid from 5·2 to 2·0 ml/h ($P < 0{\cdot}001$). Serum levels of TNF-α and IL-8 were reduced significantly in the treated group from 5 min up to 9 h after induction of ANP. The leucopenia observed after 3 h in the untreated group was not significantly improved in the group treated with sodium fusidate ($P = 0{\cdot}055$). By contrast, both treated and untreated rabbits had similar biochemical changes including levels of amylase, lipase, glucose and calcium as well as similar histological changes in the pancreas and lungs.

Conclusion Pretreatment with sodium fusidate resulted in a considerable reduction in mortality rate and ascitic fluid output in rabbits with bile-induced ANP, probably by lowering the TNF-α and IL-8 blood levels. However, pretreatment with sodium fusidate did not alter the local or systemic manifestations of ANP. Thus, cytokines other than TNF-α and IL-8 are likely to mediate the local and systemic symptoms of ANP.

Acute necrotizing pancreatitis (ANP) is a common and potentially fatal disease. Physiological derangement and multiple organ failure frequently complicate the condition, leading to high morbidity and mortality rates[1].

Similarities between the clinical syndromes of sepsis and severe ANP have focused research efforts on the identification of common mediators of the systemic complications of these diseases[2]. Activated leucocytes and proinflammatory cytokines (e.g. interleukin (IL) 1, tumour necrosis factor (TNF) α and IL-8) have been extensively reported to play a critical role in sepsis and major trauma, mediating the development of systemic complications[3]. The same mechanisms are being increasingly implicated in the pathogenesis of ANP and its associated systemic manifestations[4,5]. These cytokines would be expected to act locally to aggravate the pancreatitis, and both locally and systemically to increase vascular permeability and promote leucocyte migration and endothelial extravasation[6].

New therapies designed to downregulate this aberrant response by blocking the release or actions of these cytokines are being investigated in different models of experimental ANP. Studies from this laboratory showed that the application of either IL-10 agonist (IT 9302) or a monoclonal anti-IL-8 antibody (WS-4) to rabbits before the induction of AP diminished significantly the inflammatory response in the lungs and improved animal survival, presumably through reduction of serum levels of TNF-α and IL-8[7,8]. Earlier reports demonstrated similar results following the administration of anti-TNF-α antibody or IL-1 receptor antagonist in murine models of ANP[9,10].

Fusidic acid is a tetracyclic triterpenoic acid with a primary steroidal structure but without glucocorticoid effect. Both fusidic acid and its sodium salt have been used as an antistaphylococcal antibiotic[11]. Recently, sodium fusidate has been reported to have anti-inflammatory and immunosuppressive properties[12], interfering with various functions of the cytokines, including antagonism of IL-1 and IL-6[13]. In addition, sodium fusidate has been shown to protect D-galactosamine-sensitized mice from *Staphylococcus aureus* enterotoxin B- or lipopolysaccharide-induced death, probably by suppressing the release of TNF-α and interferon (IFN) γ[14].

The purpose of this study was to investigate the potential effects of pretreatment with sodium fusidate on the outcome of experimental ANP induced by the injection of 5 per cent chenodeoxycholic acid into the pancreatic duct in rabbits. This model of ANP is characterized by overproduction of TNF-α and IL-8, and distant organ involvement[15].

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Materials and methods

Animals

Adult male and female New Zealand White rabbits weighing 3·9–5·2 kg were used in the experiment. The animals were housed at the animal farm of Aarhus University for at least 1 week before use, according to the requirements for animal care stipulated by the Danish Experimental Animal Committee, which also approved the experimental protocol.

Anaesthesia and surgical procedures

Animals were fasted overnight with free access to tap water. They were anaesthetized with a mixture of midazolam 2 mg/kg and Hypnorm (fentanyl–fluanisone 0·3 mg/kg; Janssen, Copenhagen, Denmark), both injected intramuscularly. The animals were kept anaesthetized throughout the experimental period of 12 h by repeated injections of Hypnorm 0·15 mg/kg every hour. The operative procedures have been described in detail elsewhere[15]. Briefly, all rabbits underwent a 4-cm midline laparotomy, and the pancreatic duct was visualized entering the duodenum at a point approximately 20 cm from the pylorus. The duct was cannulated using a 24-G polyethylene catheter inserted through a small cut-down in the intramural portion of the duct at the duodenal level. AP was induced by retrograde intraductal injection of 2·0 ml 5 per cent chenodeoxycholic acid (clear faint yellow solution at 200 mg plus 4·0 ml ethanol; Sigma Chemical Company, St Louis, Missouri, USA) for 2·5 min (i.e. in a pressure-, volume- and time-controlled manner). The injection pressure was controlled with pressure recording and never exceeded 30 cmH_2O. After injection, the catheter was removed, the pancreatic duct was ligated and the abdomen was closed in two layers.

Experimental protocol

A total of 20 rabbits was allocated into two groups. The control group ($n = 10$) underwent intraductal injection of 2·0 ml 5 per cent bile acid followed by duct ligation and a subcutaneous bolus injection of 0·9 per cent saline (4·0 ml) followed by intravenous infusion of 40 ml 0·9 per cent saline for 30 min before the induction of ANP. The treated group ($n = 10$) was pretreated with sodium fusidate (Fusidin; Leo, Copenhagen, Denmark) in two doses; the first dose (80 mg/kg) was injected subcutaneously and the second dose (80 mg/kg diluted in 40 ml saline; 40 ml per 30 min) intravenously, both 30 min before the injection of 5 per cent bile acid.

Arterial blood samples were drawn at −30 min, +5 min, 3 h, 6 h, 9 h and 12 h after induction of ANP for determination of leucocyte count and levels of glucose, calcium, amylase, lipase, IL-8 and TNF-α. The volume of each blood sample (6·0 ml) was replaced by 0·9 per cent saline. Physiological saline was infused in all animals at 4 ml/h throughout the experiment. All blood samples, except blood for measurement of leucocyte count, were immediately centrifuged at 3000 r.p.m. for 10 min at 5°C. The supernatants were separated using sterile pipettes. All samples were coded and stored at −80°C pending assay.

At the end of the observation period, all surviving rabbits were killed without recovery from anaesthesia, and the ascitic fluid volume was measured by absorption of the fluid into preweighed dried towels. The towels were reweighed and the volume was calculated assuming that 1 g of fluid is equivalent to 1 ml. The total volume was divided by the hours of survival and expressed as millilitres per hour. Aliquots were separated for determination of amylase and lipase. In all animals the pancreas, lungs and kidneys were excised and fixed in 10 per cent formalin for histological examination.

Analysis

Leucocyte count was measured in ethylenediamine tetra-acetic acid-preserved blood samples using a Coulter Counter model T890 (Coulter Electronics, Luton, UK).

Serum glucose and calcium were measured by an enzymatic glucose oxygenation–dehydrogenation method and photometry respectively. Serum and ascitic fluid amylase and lipase were measured by photometry and the enzymatic reaction kinetic turbidimetry respectively.

Serum levels of TNF-α were determined with an enzyme-linked immunosorbent assay (ELISA) kit from Genzyme (Hellerup, Denmark), according to the manufacturer's guidelines. IL-8 measurement in rabbit serum was carried out with an IL-8 ELISA kit, a kind gift from Professor K. Matsushima, Tokyo, Japan. The method has been published in detail elsewhere[16], but with slight modification. Briefly, monoclonal anti-IL-8 WS-4 antibody (1·5 μg/ml) and peroxidase-conjugated antiguinea pig antibody (PO 141; DAKO, Copenhagen, Denmark) were used as capture and detection antibodies respectively.

Histological examination

Paraffin-embedded sections from the pancreas, right lung and right kidney were stained with haematoxylin and eosin. Sections of lung and kidney were further stained for fibrin (Picro Mallory) and lung sections also for elastic tissue (Orcein-van Gieson). All sections were evaluated blindly. The specimens were scored for necrosis, inflammatory cellular infiltration and the presence of vascular thrombosis according to the following criteria.

Pancreas. The volume fraction of necrotic pancreatic parenchyma was determined by point counting on haematoxylin and eosin-stained sections and expressed as necrotic tissue/total pancreatic parenchyma × 100. The part of the pancreas (one-third to one-half) that was fixed in formalin was divided longitudinally and both halves were paraffin embedded. Counting was performed by one pathologist on the entire area of a haematoxylin and eosin-stained section from each piece using an Olympus (Kyoto, Japan) microscope connected to a screen by a video camera. Objective magnification was × 4 and each field of vision contained 36 points. Sections from the pancreas of five sodium fusidate-treated animals were recounted and the intraobserver coefficient of variation was found to be 6·7 per cent. The inflammatory response to necrosis was evaluated semiquantitatively as follows: grade 0, absent; grade 1, slight focal inflammation; grade 2, moderate granulocyte margination of necrosis; grade 3, widespread and pronounced granulocyte margination of necrosis. The amount of fat necrosis was also semiquantified: grade 0, absent; grade 1, less than one-third of peripancreatic fat showing necrosis; grade 2, from one-third to two-thirds of fat with necrosis; grade 3, more than two-thirds of the peripancreatic fat showing necrosis. Finally, the presence or absence of vascular thrombosis was also determined.

Lung. In haematoxylin and eosin-stained sections from each animal the degree of oedema was semiquantified: grade 0, none; grade 1, slight oedema of the alveolar walls; grade 2, moderate oedematous thickening of alveolar walls with occasional alveoli containing coagulated oedematous fluid; grade 3, extensive occurrence of alveolar and interstitial oedema. The number of neutrophils per high-power field (× 750) was counted in ten random fields of alveolar lung tissue, avoiding fields containing bronchi or larger vessels. The presence of margination of neutrophils in vascular lumen was also noted. In some animals (sham operated[15], as well as animals with experimental ANP) focal interstitial mononuclear infiltrates were found in the lungs. These changes were ascribed to an asymptomatic infection with *Bordetella bronchiseptica* which can regularly be cultured from the airways of laboratory rabbits and is known to cause such infiltrates[17]. The infiltrates were semiquantified as follows: 0, none; 1, few; 2, moderate; 3, pronounced. In sections stained for fibrin, the presence or absence of capillary thrombosis or thrombosis of larger vessels was noted.

Kidney. In sections stained for fibrin, the presence or absence of glomerular microthrombosis was determined.

Statistical analysis

Results are expressed as mean(s.e.m.). Differences between control and treatment groups were judged by the unpaired Student *t* test for parametric data and the Mann–Whitney rank sum test for non-parametric data. $P<0.05$ was considered significant.

Results

Survival

In the control group, six animals died 6–9 h before the end of the experiment, whereas in the treatment group three animals died before the end of the 12-h observation period ($P<0.05$).

Serum amylase and lipase

All animals manifested increased levels of serum lipase throughout the observation period (*Fig. 1*). Values for serum amylase were similar. Sodium fusidate pretreatment did not affect significantly the levels of serum amylase or lipase.

Serum glucose and calcium

Serum calcium decreased steadily with time in both groups; there was no significant difference between the groups at any time (data not shown). Similarly, no significant differences in blood glucose levels were observed between the two groups. Hyperglycaemia was noted in both groups up to 9 h after induction of ANP (data not shown). However, at 12 h blood glucose level was significantly below basal level in the control group ($P<0.05$).

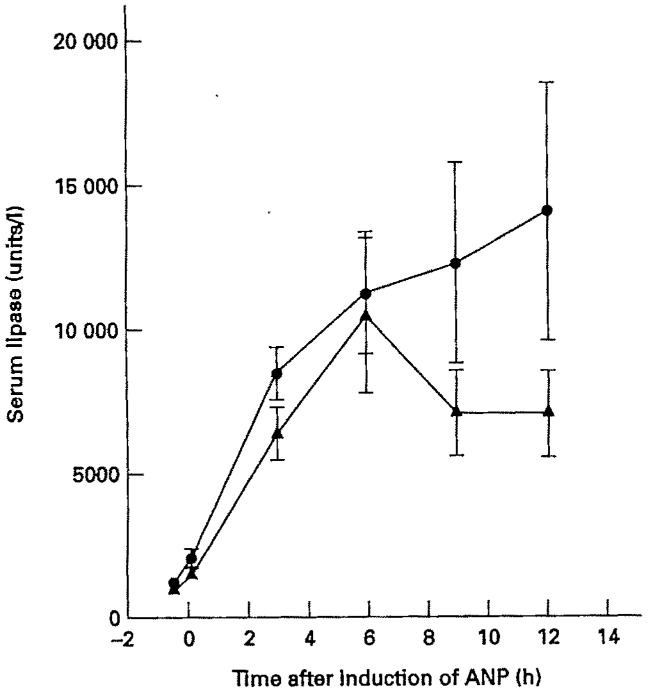

Fig. 1 Mean(s.e.m.) serum lipase levels after induction of acute necrotizing pancreatitis (ANP) in rabbits pretreated with sodium fusidate (●) and controls (▲). There was no significant effect of sodium fusidate at any time (Student *t* test or Mann–Whitney *U* test)

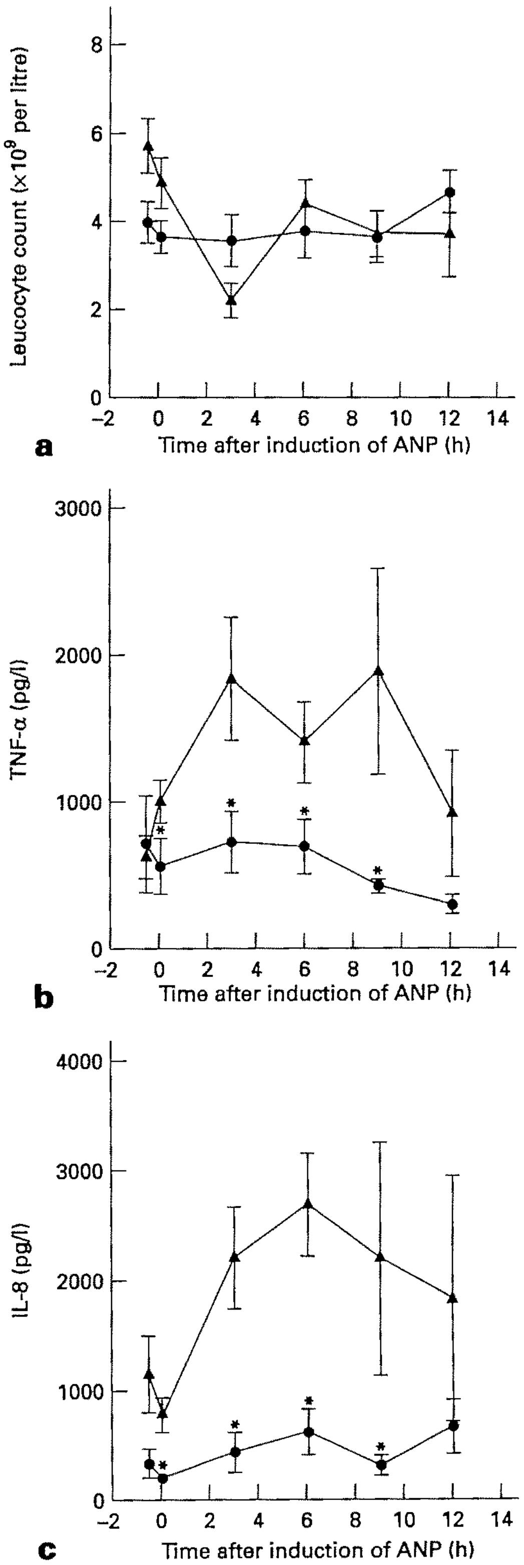

Fig. 2 Mean(s.e.m.) values for a leucocyte count, b, serum tumour necrosis factor (TNF) α level and c serum interleukin (IL) 8 level after induction of acute necrotizing pancreatitis (ANP) in rabbits pretreated with sodium fusidate (●) and controls (▲). $^*P<0.05$ *versus* control (Student *t* test or Mann–Whitney *U* test)

Leucocyte count and serum cytokines

Control animals were significantly leucopenic at 3 h. In the treated group, the leucocyte count was unchanged by that time, but the difference between the two groups was not significant ($P = 0{\cdot}055$) (*Fig. 2a*). In the control group, a significant increase in serum levels of TNF-α (*Fig. 2b*) and IL-8 (*Fig. 2c*) above basal values was noted. Pretreatment of animals with sodium fusidate resulted in a significant reduction in TNF-α and IL-8 levels compared with controls at 5 min, 3 h, 6 h and 9 h ($P < 0{\cdot}05$).

Ascitic fluid

Pretreatment of animals with sodium fusidate significantly diminished the output of ascitic fluid ($P < 0{\cdot}001$) (*Fig. 3*). By contrast, sodium fusidate did not alter the concentration of amylase or lipase in ascitic fluid (*Fig. 3*).

Histological findings

Pancreas. In both groups of animals, there was the same degree of widespread parenchymal coagulative necrosis in the pancreas (mean volume of necrotic tissue 73·5 per cent in controls *versus* 68·8 per cent in the treated group). Likewise, there seemed to be no difference between the two groups as regards the inflammatory response in the pancreas (*Table 1*). No correlation was found between survival and the severity of inflammation.

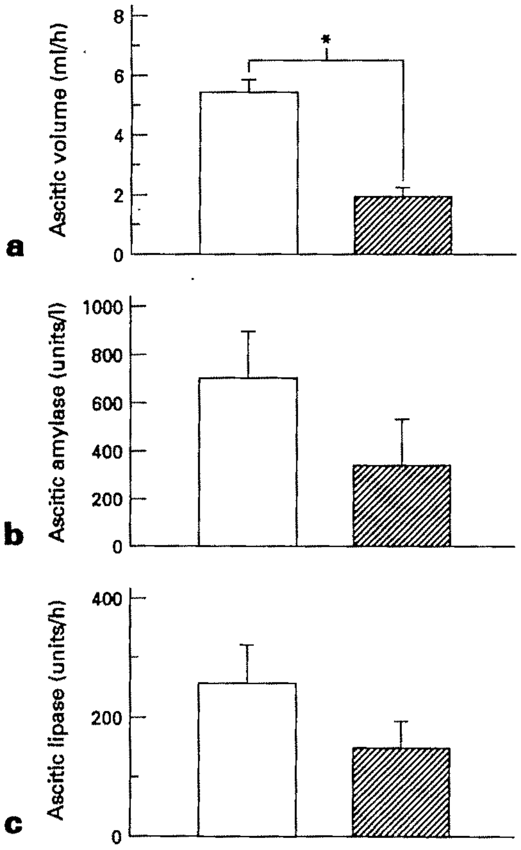

Fig. 3 Mean(s.e.m.) values for a output of ascitic fluid, and concentration of b amylase and c lipase in the ascitic fluid after induction of acute necrotizing pancreatitis in controls (□) and in rabbits pretreated with sodium fusidate (▨). $^*P < 0{\cdot}001$ (Student *t* test or Mann–Whitney *U* test)

Table 1 Effect of sodium fusidate on pancreatic histopathological grading in rabbits with acute necrotizing pancreatitis

	Neutrophil infiltration		Fat necrosis	
	Controls	Sodium fusidate	Controls	Sodium fusidate
Grade 0	2	2	0	0
Grade 1	3	3	5	4
Grade 2	2	3	4	5
Grade 3	3	2	1	1

Values are numbers of rabbits

The same was true for the degree of fat necrosis (*Table 1*). Thrombosis of pancreatic vessels was found in six of ten animals in the control group and eight of ten in the treated group.

Lung. Severe to moderate oedema as well as a pronounced infiltrate of neutrophils in the alveolar walls was observed in the lungs of control animals. These changes were not significantly changed by sodium fusidate pretreatment. The neutrophils were scattered diffusely throughout the lung tissue and were not particularly related to the interstitial mononuclear infiltrates. These mononuclear infiltrates were demonstrated in almost all animals of the two groups. In nine of ten animals in the control group and eight of ten animals in the treated group, more or less pronounced leucocytic vascular margination and perivascular infiltration of neutrophils were noted. Foci of vascular thrombosis in large vessels and/or microthrombi were noted in the control group (six of ten) and the treated group (three of ten).

Kidneys. In the control group, six of the animals showed glomerular microthrombi while none of the animals in the treated group showed signs of vascular thrombosis ($P < 0{\cdot}05$). In other respects, the kidney appeared normal.

Discussion

The present data show that pretreatment with sodium fusidate significantly decreases peak circulating TNF-α and IL-8 levels, reduces ascitic fluid output and improves animal survival for 12 h after the induction of ANP in rabbits. By contrast, sodium fusidate did not alter either the histological picture of pancreatitis or the inflammatory response in the lungs, as demonstrated by granulocyte infiltration and the degree of oedema in the lung interstitial tissues. There was no chemical interaction between sodium fusidate and the antibodies used since addition of sodium fusidate to the assay system did not have any effects on results (unpublished data). Thus, the decrease in serum TNF-α and IL-8 levels after pretreatment with sodium fusidate represents a true decrease in circulating levels and not simply an interference with the assay.

These findings suggest that the beneficial effect of sodium fusidate on animal survival is due, at least in part, to the drug's ability to decrease TNF-α and IL-8 production *in vivo*. This assumption is in agreement with previous studies in adult and neonatal murine models of septicaemia, in which sodium fusidate protected adult[14] and neonatal[18] mice against both lipopolysaccharide- and *S. aureus* enterotoxin B-induced shock. Sodium fusidate has been shown to diminish the secretion of T and B cell stimulatory cytokines such as IL-1β, IL-2 and IFN-γ, and also inhibits the thymocyte co-stimulatory activity of IL-1α, IL-1β and IL-6[14]. Subsequently, fusidic acid has been found to influence the course of immunoinflammatory disorders such as chronic endogenous uveitis[19], Behçet's colitis[20], Crohn's disease[21] and insulin-dependent diabetes mellitus[14].

Activated leucocytes and inflammatory cytokines have recently been suggested to play a predominant role in the propagation of ANP and to be responsible for death in this disease[22]. Serum levels of TNF-α, IL-6 and IL-8 are raised in patients with complicated ANP, correlating positively with the incidence of systemic complications and increased mortality rate[4–6]. The beneficial effects of sodium fusidate on survival and the reduction of ascitic fluid output, which are most likely to occur directly or indirectly through cytokine inhibition, further support the hypothesis implicating cytokines in the pathogenesis of ANP. Anticytokine therapeutic trials, especially of anti-TNF-α, are now being developed to modify the inflammatory response in ways presumed to be advantageous to an injured host[9,23]. However, the preliminary results of such trials seem to be conflicting, with largely speculative explanations[24,25].

At the same time, there exists a large body of literature addressing the role of neutrophil activation in the pathogenesis of ANP[4,22]. However, it is still a matter of controversy as to what induces leucocyte activation during ANP. It may be simply the amount of pancreatic necrosis, the various bacterial products or the presence of different potent chemokines[4]. Recently, IL-8 has been characterized as a potent and selective neutrophil- and T cell-activating and chemotactic cytokine[26]. IL-8 serum levels have been reported to be raised in patients with severe ANP, correlating positively with the severity of the disease and with serum levels of both neutrophil elastase[27] and C-reactive protein[28]. Blocking the effects of IL-8 by a specific monoclonal anti-IL-8 antibody (WS-4) reduced significantly the inflammatory response in the lungs, diminished the output of the ascitic fluid and improved animal survival in a rabbit model of ANP[8]. Clinically, the administration of lexipafant, a platelet-activating factor antagonist, reduced organ dysfunction and suppressed serum levels of IL-8 in patients with ANP[29,30].

It has been reported that bile salts are very potent stimuli of oxygen free radical production and that detergents and crystals in bile could be extremely powerful chemotaxins[31]. This observation might account for the severity of pancreatitis in the present model and the negligible effect of sodium fusidate pretreatment in spite of cytokine inhibition. In addition, the presence of other inflammatory mediators not influenced by the administration of sodium fusidate might also explain these findings. However, the present study was designed not as a treatment study but as a pathophysiological study. This was the reason for pretreatment with sodium fusidate instead of treatment with sodium fusidate after induction of ANP, and the study period was long enough for the aims of the study, i.e. to clarify the initial effects of sodium fusidate on the physiological derangement seen during ANP in its early stage. As a result of the present findings it would seem obvious to test, experimentally, the effect of sodium fusidate administered after the induction of ANP on clinical outcome.

Sodium fusidate is a potent immunosuppressor[12] modulating the functions of various cytokines with low toxicity[11]. Its application to modify the cytokine changes in ANP is a logical therapy and/or prophylactic method for use in conjunction with procedures known to induce acute pancreatitis clinically, such as endoscopic retrograde cholangiopancreatography. The present study demonstrates the feasibility of modulating circulating levels of TNF-α and IL-8, and supports the hypothesis that raised levels of these cytokines are associated with fatal outcome.

Acknowledgements

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Short note

Treatment of irresectable liver tumours by percutaneous cryosurgery

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Cryosurgical treatment of liver tumours is used increasingly when conventional surgical excision cannot be performed, or as an adjunct to surgical resection when clearance is restricted by anatomical limitations, such as proximity to the main hepatic vessels. This technique is safe and potentially curative, at least in patients with small hepatic tumours[1–4]. One of the main drawbacks, however, is the need for a conventional surgical incision, to direct the probe into the tumour along a course that minimizes parenchymal damage, to monitor accurately the freezing process with ultrasonography and to control bleeding from the intrahepatic course of the probe.

Improvements in the engineering of cryosurgical tools and the experience gained in the open cryosurgical treatment of liver tumours have allowed the development of percutaneous cryosurgery. The present report includes experience with three patients, describing the technical aspects and outcome of percutaneous cryosurgery.

Patients and methods

Percutaneous cryosurgery was considered in patients with a solitary primary or secondary malignant liver tumour that was easily detectable by conventional ultrasonography, preferably in the anterior segments of the liver (segments 2, 3, 4, 5 and 8), and in whom there was a contraindication to surgical resection.

Cryosurgery was performed with an LCS 2000 apparatus (Spembly Medical, Andover, UK; Candela Corporation, Wayland, Massachusetts, USA) and a specifically designed probe 3 mm in diameter. The engineering characteristics of the probe were similar to those of the 5- and 10-mm probes used for the open technique[4].

Under general anaesthesia, the probe was inserted under ultrasonographic guidance into the central part of the tumour. Two freeze–thaw cycles were performed, each of sufficient duration to allow the temperature at the tip of the probe to reach − 196°C and the formation of an 'ice ball' visible as a hypoechoic area exceeding the diameter of the lesion by 1 cm. The skin at the puncture site was protected by either a plastic sheath (first patient) or surgical gauze swabs soaked with warm saline (latter two patients). The cryoprobe was removed as soon as the tip temperature reached 0°C so as to minimize bleeding from the probe track (experience from open cryosurgery showed that bleeding from the puncture site on the surface of the liver occurs mainly on rewarming of liver tissue).

Patients were kept in hospital for a minimum of 48 h after the procedure, with three daily haematocrit measurements for the first day and with full blood count and liver function testing daily. Follow-up monitoring consisted of spiral computed tomography with arterial (30 s) and venous (120 s) acquisition phases at 1, 3 and 9 months, ultrasonography and determination of a tumour marker (α-fetoprotein (AFP) or carcinoembryonic antigen).

Results

Patient 1

A 58-year-old man with hepatitis B virus cirrhosis presented with hepatocellular carcinoma (HCC) in segment 4. The diameter of the tumour decreased from 14 to 6 cm and serum AFP levels from 30 000 ng/ml to the normal range (less than 9 ng/ml) after five treatments of transarterial chemoembolization. Liver resection was refused by the patient and percutaneous cryosurgery was performed. The postoperative course was uneventful. An increase in the level of aspartate aminotransferase (ASAT) to 111 (normal value less than 35) units/l and of alanine aminotransferase (ALAT) to 124 (normal value less than 43) units/l was observed, with a temporary fall in prothrombin time from 100 to 78 per cent of the control value, and a reduction in the platelet count from 185 to 144×10^9/l. The patient was discharged home on day 2 with decreasing transaminase concentration. At the last follow-up visit (3 years after the procedure) a visible lesion, 45 mm in diameter with calcification seen on ultrasonography, was considered to represent scar tissue. Serum AFP levels remained normal.

Patient 2

A 69-year-old man with alcoholic cirrhosis, a previous splenorenal shunt and two hepatectomies for HCC presented with a recurrent nodule (2·5 cm) in segment 8. Percutaneous cryosurgery was performed instead of resection because of difficulties likely to arise following the three previous operations. The postoperative course was uneventful. An increase in serum transaminase concentrations on day 2 (ASAT 280 units/l, ALAT 219 units/l), a decrease in prothrombin time to 71 per cent of the control value and a reduction in the platelet count (125×10^9/l) were resolving by the time of discharge on day 3. There were no signs of local recurrence at the last outpatient visit, 12 months after the procedure.

Patient 3

A 70-year-old woman with a history of colorectal cancer presented with recurrent liver metastasis in close contact with the right portal branch (2·7 cm in segments 5 and 8). She had previously had a left hepatic lobectomy and a repeat liver resection in segment 6. Further operation would have required an excessive sacrifice of liver tissue, so percutaneous cryosurgery was performed. The postoperative course was uneventful with a moderate increase in transaminase levels (ASAT 503 units/l, ALAT 465 units/l), a decrease in prothrombin time from 84 to 69 per cent of the control value and a reduction in the platelet count from 103 to 57×10^9/l. The patient was discharged home on day 4 with decreasing transaminase

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levels. No signs of local recurrence were present 13 months after the procedure.

Discussion

In the initial experience with percutaneous cryotherapy, suitable lesions were selected, namely solitary tumours that were easily visible on ultrasonography and readily accessible with a percutaneous probe. Proximity of the main portal or hepatic vessels was not considered a contraindication as these structures are to some extent protected from freezing by the warming effect of their high blood flow. No attempt was made to spare the main biliary branches; the risk of damage during cryotherapy of deep lesions is probably smaller than when main biliary structures are exposed to surface cryotherapy. No abnormalities of the vascular or biliary tree were found on ultrasonography at follow-up.

The risk of bleeding was minimized by the engineering of a small probe (3 mm) and by removing it as soon as a temperature of 0°C was reached. Furthermore, the contact with the parietal peritoneum may have diminished the bleeding commonly seen during open cryosurgery. The use of gauze swabs soaked in warm saline was adequate to protect the skin; the coaxial plastic sheath introduced an air artefact which impeded optimal cryotherapy. In the three patients the technical feasibility of the procedure (i.e. reaching the target and monitoring the 'ice ball' by ultrasonography) was no more difficult than with the open approach. No complications were observed, allowing hospital discharge within 4 days. The skin healed normally at the probe entry site and no local recurrence has been detected, although the duration of follow-up is still short.

The efficacy of percutaneous cryosurgery in the management of irresectable liver tumours merits further investigation and must now be compared with other minimally invasive treatments. Ethanol injection can be used only for HCC because the diffusion of the agent is dependent on the physical characteristics of the tumour and surrounding liver[5,6]. Compared with radiofrequency ablation, percutaneous cryosurgery allows visual monitoring of the area of tissue destruction.

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Preoperative duplex imaging is required before all operations for primary varicose veins

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Background Physical examination is unreliable in the detection of sources of reflux in varicose veins. Hand-held Doppler (HHD) ultrasonography has been recommended as an accurate adjunct to physical examination. The aim of this study was to evaluate the accuracy of HHD imaging in comparison with duplex ultrasonography.

Methods Eighty-nine legs in 61 patients with primary varicose veins were examined with an HHD probe to detect reflux at the saphenofemoral junction (SFJ), the saphenopopliteal junction (SPJ) and in thigh perforators (TPs). Patients then underwent duplex imaging and the results of the tests were compared.

Results The sensitivity of the HHD technique was 73 per cent at the SFJ, 77 per cent at the SPJ and 51 per cent for TPs. In primary varicose veins the surgery planned using HHD imaging alone would have left residual sites of reflux in 24 per cent.

Conclusion Examination with HHD ultrasonography is not sufficiently accurate to plan varicose vein surgery. Duplex imaging is recommended before all operations for primary varicose veins.

Operations for varicose veins are among the commonest in general and vascular surgery. Up to 25 per cent of women and 15 per cent of men have visible varicose veins[1]. Recurrence of varicose veins occurs in significant numbers of patients. This may occur as a result of disease progression, failure to eradicate sites of reflux at primary surgery or reflux into a patent long saphenous vein (LSV) through an inadequately explored saphenofemoral junction (SFJ) or via neovascularization[2–4]. Recurrence can be reduced substantially by stripping the LSV to the level of the knee[2,3,5]

Considerable variation exists in the reported prevalence of SFJ, thigh perforator (TP) and saphenopopliteal junction (SPJ) incompetence[6–9]. Careful preoperative assessment of the contribution of each system is required to target sites of reflux for surgery.

Traditional clinical examination using Trendelenburg and tourniquet testing is unreliable[10,11]. Hand-held Doppler (HHD) ultrasonography is a more accurate method of detecting sites of reflux[6,12,13]. Colour duplex ultrasonography is an accurate non-invasive investigation for the assessment of varicose veins[9,14,15] which combines an image and a Doppler signal.

Comparison of results from the two investigations allows identification of patients in whom an operation based on the findings of the HHD technique alone would have resulted in ligation of a competent and functioning element of the venous system, or would have left a site of incompetence intact and therefore, perhaps, at greater risk of early recurrence.

As in previous studies[11,13,16,17] and investigations of other aspects of venous haemodynamics[2,3,15,18,19], colour duplex imaging by an experienced vascular radiologist has been defined as an accurate gold standard.

Patients and methods

Sixty-one patients with primary varicose veins affecting 89 legs were assessed by a consultant vascular surgeon (D.J.A.S. or D.C.B.) in a specialist venous outpatient clinic.

The distribution of the varicosities was recorded after each examination using an 8-MHz HHD probe (Dopplex; Huntleigh, Luton, UK) and a 4-MHz probe in the popliteal fossa using a standard protocol. The patient was asked to stand facing the surgeon with the leg slightly flexed and the weight on the opposite limb. The SFJ was located according to surface markings. With the probe held over the junction a calf squeeze was applied and released. This process was repeated in the popliteal fossa to examine the SPJ using a 4-MHz probe, and over the LSV at the level of the knee. Audible reflux at either the SFJ or SPJ lasting longer than 0·5 s was deemed to indicate incompetence. If there was no evidence of SFJ incompetence, but reflux was detected in the LSV, the HHD probe was used in combination with intermittent calf compression to trace the course of the LSV to identify sites of any incompetent TPs. A standard form was used to record the clinical findings.

At a separate appointment each patient underwent venous duplex imaging by a consultant vascular radiologist. The results of the HHD examination were recorded on the request card and therefore known to the radiologist. Colour flow duplex ultrasonography using a Siemens Quantum 2000 (Siemens Medical, Issaquah, Washington, USA) or B&K 3535 (B&K Medical, White Waltham, UK) with Acuson 128 5-MHz curvilinear probe (Mountain View, California USA) was used to identify abnormal deep to superficial venous reflux on release of a calf squeeze in the unweighted limb. Incompetence was defined as reflux lasting longer than 0·5 s. Duplex assessment was used as the 'gold standard' to assess the accuracy of the HHD probe in determining sites of reflux.

Results

Duplex imaging

Reflux was detected at the SFJ in 59 legs (66 per cent), at the SPJ in 26 (29 per cent) and at a TP in 35 (39 per cent) using duplex imaging. Twenty-two legs (25 per cent) had

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more than one site of reflux and in three (3 per cent) no site of reflux was demonstrated.

Hand-held Doppler probe

The findings of examination using HHD compared with those at the subsequent duplex scan are summarized in *Table 1*. The sensitivity of the HHD technique was similar at the SFJ (73 per cent) and SPJ (77 per cent), and was worse for TPs (51 per cent). In comparison, false-positive results were rare, giving specificities of 93 per cent (SFJ), 94 per cent (SPJ) and 85 per cent (TP) (*Table 2*).

Planning venous surgery for primary varicose veins

Using SFJ or TP reflux as an indication for SFJ ligation and stripping of the LSV, and SPJ incompetence as an indication for SPJ ligation, an assessment of the accuracy of the HHD probe for operative planning was made (*Table 3*). In 71 per cent of the examined legs (63 legs) the operative procedure suggested by HHD ultrasonography agreed with that indicated by duplex imaging. In five legs (6 per cent) the HHD result suggested surgery to an entirely competent system and in 19 legs (21 per cent) the operation suggested by HHD would have left an incompetent system intact. In two legs (2 per cent) a combination of inappropriate and inadequate surgery would have been performed on the basis of the HHD findings.

Table 1 Comparison of findings using the hand-held Doppler probe and duplex imaging

	Incompetent on duplex		Competent on duplex	
HHD	Reflux detected	No reflux detected	Reflux detected	No reflux detected
SFJ	43	16	2	28
SPJ	20	6	4	59
TP	18	17	8	46

Values are the number of legs. HHD, hand-held Doppler ultrasonography; SFJ, saphenofemoral junction; SPJ, saphenopopliteal junction; LSV, long saphenous vein

Table 2 Accuracy of the hand-held Doppler probe at sites of reflux in 89 legs

	SFJ	SPJ	TP
Sensitivity (%)	73 (58–84)	77 (53–90)	51 (32–69)
Specificity (%)	93 (74–97)	94 (82–97)	85 (70–93)

Values are percentages (95 per cent confidence intervals). SFJ, saphenofemoral junction; SPJ, saphenopopliteal junction; TP, thigh perforator

In 53 legs in which HHD ultrasonography suggested that high tie and stripping of the LSV were required, duplex imaging revealed that six (11 per cent) were incorrectly assessed. In three there was no evidence of reflux at the SFJ and in four reflux at the SPJ was missed.

A policy of imaging only patients with detectable popliteal reflux on HHD ultrasonography would have missed seven incompetent SPJs; this represents seven of 21 missed cases of reflux in this series.

Discussion

Varicose veins recur after primary surgery in 7–93 per cent of patients and approximately 20 per cent of those requesting surgery have had a previous operation[15,18], most commonly ligation of the SFJ with or without stripping of the LSV. Surgery for recurrent varicose veins is technically more demanding and prolonged. Recurrent varicose veins are usually due to persistent or recurrent reflux in the long saphenous system, or SPJ reflux[4,20]. Accurate SFJ ligation combined with stripping of the LSV reduces the rate of recurrence in the long saphenous system, whether due to neovascularization or TP reflux[2]. Recurrence of varicose veins should therefore be minimized by accurate preoperative determination of the sites of venous reflux and adequate surgery at these sites. It should occur only when disease progression involves a new system.

Duplex imaging is non-invasive, gives accurate anatomical information and identifies sources of reflux accurately by colour flow and waveform analysis. The technique, however, requires expensive equipment and expertise. Recommendations regarding the need for adjunctive radiological investigations depend on the accuracy and availability of the method, and the costs and risks.

It has been suggested that HHD ultrasonography is sufficiently accurate in detecting isolated LSV reflux and in excluding reflux at the SPJ that imaging is required only in patients with suspected popliteal reflux[13,16,17,21]. Salaman *et al.*[13] found a 92 per cent accuracy with the HHD probe at the SFJ but inaccuracy in the diagnosis of perforator and SPJ reflux (44 per cent sensitivity for SPJ reflux). Campbell *et al.*[16] reported 91 per cent sensitivity in detecting LSV reflux but, overall, a 72 per cent sensitivity for various types of reflux in the popliteal fossa. Only Darke *et al.*[17] have reported consistently accurate results at the SFJ (sensitivity 95 per cent, specificity 100 per cent) and SPJ (sensitivity 98 per cent, specificity 95 per cent).

Table 3 Implications of using hand-held Doppler ultrasonography for surgical planning in 89 legs

	Operation based on duplex imaging			
Operation based on HHD	Stab avulsions only	SFJ ligation and LSV strip	SPJ ligation	SPJ and SFJ ligation and LSV strip
Stab avulsions only	1	8	3	0
SFJ ligation and LSV strip	2	47	1	3
SPJ ligation	0	1	9	3
SPJ and SFJ ligation and LSV strip	0	4	0	8

HHD, hand-held Doppler ultrasonography; SFJ, saphenofemoral junction; SPJ, saphenopopliteal junction; LSV, long saphenous vein

In the present series substantial inaccuracies in the detection of sites of reflux using HHD ultrasonography have been demonstrated despite attempts to minimize interobserver and intraobserver errors by restricting assessments to two consultant vascular surgeons. A 29 per cent discrepancy in operative planning based on the findings with the HHD probe includes patients with all patterns of venous reflux and clinical findings. Twenty-four per cent of patients would have had inadequate surgery based on the findings of HHD ultrasonography. Accuracy was slightly better in the assessment of patients with reflux detectable in the LSV alone. However, one-quarter of the inaccurately assessed patients had reflux only in the long saphenous system and nine of the 27 incompetent SPJs were not detected using the HHD probe (*Table 3*).

Duplex imaging also gives anatomical information not provided by physical examination. Identification of the level of the SPJ is a well recognized advantage to imaging the popliteal fossa. In the long saphenous system, similar information regarding the presence and site of incompetent perforating veins is valuable.

Use of the HHD probe in the preoperative assessment of patients with varicose veins was not accurate enough to plan surgery in this series. Duplex imaging requires equipment and radiological expertise but provides accurate information, allowing the treatment of all sites of venous reflux. In a climate of limited finances and expertise, patients with reflux in the LSV alone will, as a group, benefit the least from routine imaging. However, a policy of not imaging these patients will leave sites of reflux undetected and untreated.

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Current management of acute leg ischaemia: results of an audit by the Vascular Surgical Society of Great Britain and Ireland

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Background Management of acute leg ischaemia has changed in recent years. This study aimed to elucidate current practice throughout the UK and Ireland.

Methods Surgeons and audit departments were asked to return a questionnaire about every episode of acute leg ischaemia seen in the hospital between 1 January and 31 March 1996.

Results A total of 539 episodes were reported in 474 patients (248 men) aged 19–96 (median 73) years. Common causes were thrombosis *in situ* (41 per cent), embolism (38 per cent) and graft or angioplasty occlusion (15 per cent). Vascular surgical advice was requested in 95 per cent of cases. Initial management was: immediate embolectomy in 21 per cent, anticoagulants in 13 per cent and no vascular intervention in 10 per cent. Arteriography was done in 56 per cent, followed by 186 endovascular and 165 surgical interventions. At 30 days, 70 per cent of limbs were definitely viable and 16 per cent had been amputated. The mortality rate was 22 per cent. Cases were reported by 86 of 182 hospitals contacted, but some referred no patients, and a supplementary audit of 54 cases (10 per cent size of the original sample) from non-contributing hospitals showed no important differences.

Conclusion Patients with acute leg ischaemia are generally treated by vascular specialists, with modern methods and acceptable results. This is being achieved despite insufficient vascular surgeons and radiologists for formal emergency rotas in most hospitals.

The management of acute leg ischaemia has changed progressively over the past three decades, with radical developments in the approach to treatment during recent years. The balloon embolectomy catheter was described in 1963[1] and became the cornerstone of management through the 1960s and 1970s[2,3]. Embolectomy remains the best method for treating embolism with a white insensitive limb, but poor results in patients with thrombosis were increasingly recognized in the late 1970s and early 1980s[4–9]. It was realized that embolectomy might need to be supplemented by arteriography[4,7], reconstruction[5,6,8–10] or the use of thrombolytic agents[11–16], especially in the setting of chronic arterial disease with thrombosis *in situ*. More recently, catheter-directed thrombolysis has become commonplace as the primary management of acute leg ischaemia[17–22]. Urgent arteriography is now often recommended for all patients as a prelude not only to thrombolysis, but to the possibilities of balloon angioplasty, stenting or surgical reconstruction.

These advances have necessitated an increasingly specialist approach to the management of acute leg ischaemia[23–25] by vascular surgeons working in close cooperation with specialists in vascular radiology. The fact that the patients present as an emergency, and generally require urgent treatment, has posed a problem for the many hospitals in the UK and Ireland that have insufficient vascular surgeons and radiologists for a proper emergency rota[26]. In many places these specialists have provided a service at great personal cost[27]. The extent to which patients with acute leg ischaemia are currently dealt with by vascular specialists has not been documented. Nor is it known how widely the various methods of treatment for acute leg ischaemia are used outside the few hospitals that have published their practices and results.

This study aimed to provide a picture of the current management of acute leg ischaemia in the UK and Ireland, by obtaining details of all possible patients seen in hospital during a 3-month interval.

Patients and methods

Advance notice of this study was sent to all members of the Vascular Surgical Society of Great Britain and Ireland (VSSGBI); in addition the clinical audit chairpersons of all acute hospital Trusts were contacted and asked for assistance in identifying all patients with a diagnosis of acute leg ischaemia during the interval from 1 January to 31 March 1996, irrespective of whose care they were under.

A detailed machine-readable questionnaire was designed, which was to be completed for each ischaemic leg. Ten questionnaires were sent to each hospital, with the offer of more if required. The front sheet of the questionnaire described the patients to be reported, as follows:

> Definition of acute lower limb ischaemia is very difficult. Acutely bloodless limbs with the 'six Ps' quite obviously fall within any definition, but we also want to include limbs which have become threatened acutely by ischaemia and yet failed to present to hospital for a few days. A maximum duration of two weeks since the onset of ischaemia has been chosen, but most acutely ischaemic limbs are likely to have presented after a lesser delay. Some overlap with chronic limb ischaemia is inevitable, but it will be up to individual surgeons to decide whether a limb is indeed 'acutely ischaemic' guided by the definition below. All acutely ischaemic limbs should be entered whatever the cause: this includes traumatic injury and iatrogenic causes (e.g. cardiac catheterization).

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> *Definition* A previously stable limb with sudden deterioration in arterial supply for less than two weeks. Features of acute ischaemia include rest pain, reduced sensation or movement, and tissue necrosis, due to ischaemia.

A separate questionnaire was completed for each presentation of an acutely ischaemic leg (designated an 'event'). Some patients had more than one event during the study. Questions about outcome for the leg specified information at 30 days; or at the time of death if at less than 30 days; or at discharge from hospital if at less than 30 days and if subsequent information was not available.

Completed questionnaires were scanned on to FORMIC 2 (FORMIC, London, UK), and the data were analysed with SNAP version 3 (Mercator Computer Systems, Bristol, UK). Not all questions were answered for every patient, and percentages were therefore calculated using the total number of responses as denominator (not the total number of questionnaires returned).

After collation of the questionnaire responses, enquiries were made about why some hospitals had not reported any patients. In addition, a supplementary audit of unreported patients was undertaken in an attempt to establish whether there were any important differences between the patients reported in the study and those dealt with during the same interval by hospitals that had not contributed. A 10 per cent sample was analysed, gleaned from hospitals in different parts of England by one of the authors (B.M.F.R.), who visited each hospital, with permission, to obtain full details of patients.

Statistical testing for differences between groups (including differences between this main audit and the supplementary audit) was by χ^2 analysis.

Results

Patients were reported from 86 of 182 hospitals contacted. Eleven responded but had no patients, and 85 did not respond at all. Enquiries revealed that 26 of the non-responders referred all patients with acute leg ischaemia elsewhere; one had been 'duplicated'; one was twinned with another unit that had contributed; and one was not an acute admitting hospital. Taking account of these 29, a total of 56 hospitals that might have treated patients with acute leg ischaemia failed to contribute. *Table 1* shows the geographical distribution of contributing hospitals. Some explanation for failure to contribute was provided by 73 individual VSSGBI members who had written giving reasons for reporting no cases: no suitable patients (20), various reasons for not completing forms (for example, 'form too long') (29), and denial that forms had been received (although a second set was sent automatically) (24).

Questionnaires were returned describing 539 events in 474 patients. There were 248 men and 226 women, aged 19–96 (median 73) years. The 64 patients with acute ischaemia of both legs comprised 14 per cent of the patients. Similar numbers of right (237) and left (238) legs were affected.

Most patients developed acute leg ischaemia at home and were admitted to hospital under the care of a vascular surgeon (*Tables 2* and *3*). Vascular surgical advice was requested in 460 (95 per cent) of 486 events (not recorded in 53), and was provided without delay in 362 (79 per cent). In 101 (22 per cent) there was considered to have been delay in obtaining vascular surgical advice, but this was attributable to the vascular team on only 15 (15 per cent) occasions (*Table 4*).

The cause of acute ischaemia was thought to be thrombosis *in situ* in 206 events (41 per cent), embolism in 191 (38 per cent), occlusion of a bypass graft or angioplasty site in 77 (15 per cent), thrombosis of a popliteal aneurysm in 13 (3 per cent), trauma in 11 (2 per cent) and iatrogenic in ten (2 per cent).

Table 1 Geographical distribution of hospitals that reported cases

Area*	Proportion of contributing hospitals
North-West England	14 of 22
North–Central and East England	27 of 38
Scotland	7 of 11
Wales	5 of 8
South-West England	6 of 12
South-East England	21 of 47
Oxford and East Anglia	5 of 28
Northern Ireland	1 of 9
Republic of Ireland	0 of 7

*These are general geographical areas, not designated healthcare regions

Table 2 'Where was the patient at the time of onset of symptoms?

	No. of events
Own home	390 (75)
Other ward	53 (10)
Other hospital	42 (8)
Residential home	21 (4)
Nursing home	17 (3)
No reply	16

Values in parentheses are percentages

Table 3 'Under which specialty was the patient admitted to hospital?'

	No. of events
Surgeon with vascular interest	259 (55)
General surgeon without vascular interest	120 (25)
Acute general medicine	50 (11)
Care of elderly or rehabilitation	35 (7)
Orthopaedics	9 (2)
No reply	66

Values in parentheses are percentages

Table 4 Reasons given for delay in obtaining vascular advice

Reason	Percentage	No. of events*
Delay in presentation	40	
Delay by patient		13
Delay by general practitioner		12
Transfer delay		12
Delay in referral	35	
Decision by admitting team to delay referral		32
Delay by vascular team	16	
Vascular surgeon not available		13
Vascular radiologist not available		2
Other	9	
No reply		9
Wrong or uncertain diagnosis		5
Miscellaneous		3

*Nineteen replies not received were excluded

Initial management included arteriography in 297 events (56 per cent), immediate embolectomy in 111 (21 per cent), therapeutic anticoagulation alone in 70 (13 per cent) and no vascular intervention at all in 52 (10 per cent). The 45 patients who had no vascular intervention were 10 years older than the remainder (median age 83 years). Twenty-eight were desperately ill or moribund and six others had unsalvageable limbs. One had microemboli, and the reason for no intervention was not stated in the remaining 18. *Table 5* shows the initial actions after arteriography.

Table 5 Initial actions following arteriography

	No. of actions*
Conservative	
Nil or pain control	6
Anticoagulation	4
Prostacyclin	1
Total	11
Endovascular	
Thrombolysis	113
Angioplasty	61
Clot aspiration	12
Total	186
Surgical	
Bypass or endarterectomy	80
Embolectomy or thrombectomy	60
Fasciotomy	17
Primary amputation	8
Total	165

*A total of 362 actions following 297 events: some patients had more than one kind of treatment after arteriography

Embolectomy (or thrombectomy) was performed in a total of 194 events. In addition to the 111 immediate embolectomies and the 59 that were done soon after arteriography, a further 24 were performed later on (four of these were repeat embolectomies). Local anaesthesia was used for 65 (42 per cent) embolectomies, while 90 (58 per cent) were done under general anaesthesia (155 responses only). The surgical approach was femoral in 123, popliteal in ten, and directly into a bypass graft in 19. Additional procedures done at the time of embolectomy were arteriography (48), thrombolysis (18), bypass grafting (17) and fasciotomy (20).

The most senior surgeon present during embolectomy operations was a consultant in 73 (46 per cent), a senior registrar in 50 (32 per cent), a registrar in 33 (21 per cent) and a senior house officer in one (1 per cent); this senior surgeon was a member of the vascular surgical team in 94, 90, 92 and 0 per cent of operations respectively.

At 30 days after the last vascular intervention 344 (70 per cent) legs were viable, 47 (10 per cent) non-viable and 20 (4 per cent) dubious; 79 (16 per cent) had required a major amputation. The condition of 50 legs was unknown, and the question on outcome was not answered for nine patients. *Tables 6* and *7* show the outcomes after different methods of management.

By 30 days after the last vascular intervention 103 of 474 patients had died, a mortality rate of 22 per cent. *Table 8* shows the association of different types of treatment with mortality.

The relationship between mortality and outcome for the leg was evaluated. Twenty-seven (8 per cent) of 337 patients with a viable leg died, compared with 20 (26 per cent) of 77 who required major amputation, 11 (55 per

Table 6 Outcome for the leg at 30 days after the last vascular intervention*

	No vascular intervention	Anticoagulants only	Immediate embolectomy	Initial arteriography†
Viable	11 (21)	41 (59)	81 (73)	211 (73)
Dubious	4 (8)	3 (4)	2 (2)	10 (30)
Non-viable	19 (37)	10 (14)	9 (8)	9 (3)
Major amputation	9 (17)	9 (13)	15 (14)	41 (14)
Other	10 (19)	7 (10)	5 (5)	23 (8)
No reply	0	1	0	8
Total‡	52	70	111	297

Values in parentheses are percentages. *Or at time of death if at less than 30 days, or at discharge from hospital if less than 30 days and subsequent information was not available. †Outcome after the different treatments that were undertaken following arteriography are shown in *Table 7*. ‡Some respondents replied 'yes' to more than one procedure

Table 7 Outcome* for the leg at 30 days after initial arteriography, followed by different methods of treatment (or at less than 30 days as specified in Table 6)

	Thrombolysis	Bypass or endarterectomy	Angioplasty	Embolectomy
Viable	82 (69)	57 (77)	48 (76)	48 (81)
Dubious	4 (3)	1 (1)	1 (2)	0 (0)
Non-viable	5 (4)	1 (1)	1 (2)	1 (2)
Amputation	20 (17)	11 (15)	8 (13)	7 (12)
Other	7 (6)	4 (5)	5 (8)	3 (5)
No reply	1	3	1	1

Values in parentheses are percentages. *In addition to the modalities shown, 18 legs had fasciotomy (14 viable, three amputated, one 'other') and 12 had clot aspiration (nine viable, three amputated). Note that some legs had more than one procedure

Table 8 Patients who died after each type of management

	No. of deaths
Initial treatment	
No vascular intervention	24 of 52 (46)
Anticoagulation only	14 or 70 (20)
Immediate embolectomy	27 of 111 (24)
Following arteriography	
Thrombolysis	22 of 118 (19)
Angioplasty	7 of 63 (11)
Embolectomy or thrombectomy	6 of 59 (10)
Bypass or endarterectomy	5 of 77 (6)
Other treatment	11

Values in parentheses are percentages

Table 9 Comparison of the original study and the validation sample

	Original study	Validation sample
No. of episodes	539	54
Sex ratio (M:F)	283:256	30:24
Median (range) age (years)	73 (19–96)	77 (41–104)
Admitted under vascular specialist (%)	55	62
Vascular advice requested (%)	95	95
Delay in vascular advice (%)	22	2*
Initial management		
Conservative	52 (10)	2 (4)
Anticoagulation only	70 (13)	11 (20)
Conservative and anticoagulated groups combined	122 (24)	13 (24)
Immediate embolectomy	111 (21)	8 (15)
Arteriography	297 (55)	23 (43)
Viable legs at 30 days	344 of 490 (70)	29 of 45 (64)
Amputation at 30 days	79 of 490 (16)	9 of 45 (20)
Deaths	103 of 474 (22)	12 of 50 (24)

Values in parentheses are percentages unless stated otherwise. *$P < 0{\cdot}01$ (χ^2 test)

cent) of 20 with 'dubious' and 35 (76 per cent) of 46 with a 'non-viable' leg.

Supplementary audit of patients from non-contributing hospitals

The fact that no patients were reported by 56 hospitals mandated an audit to investigate the possibility that important differences might exist between patients managed in contributing and non-contributing hospitals. This supplementary audit aimed to examine a sample equivalent to 10 per cent of the number of events reported, and five hospitals provided these patients (audited in succession until sufficient events had been identified). No hospital that was approached refused to cooperate.

The hospitals selected were located in different parts of England and included four district general hospitals and one teaching hospital. Staff collaborated fully, searching computer records to identify patients who had presented during the study interval and drawing case notes for inspection. Fifty-four events were identified. The only significant difference between this sample and the main study group was in the proportion for which it was considered that there had been a delay in obtaining vascular advice (lower in the validation sample, $P < 0{\cdot}01$) (*Table 9*).

Discussion

The aim of this study was to achieve an overview of the presentation and management of acute leg ischaemia. In the event, a proportion of hospitals failed to contribute, and it is therefore fundamental to consider the representativeness of the study population before drawing any comparisons or conclusions. The supplementary audit showed no important differences from the original study, and it is therefore reasonable to conclude that the original sample was representative. A possible criticism of the supplementary audit was the fact that it did not include hospitals that treated only one or two patients. Units likely to be treating larger numbers were approached in order to limit the amount of travelling involved. It could be argued that non-contributing hospitals treating very few cases might have had worse results.

The fact than none of the seven hospitals in Ireland contributed makes the study sample applicable to the UK alone, so an estimate of the frequency of acute leg ischaemia can therefore be based on the UK population of approximately 60 million. A total of 91 hospitals contributed either to the original study or to the supplementary audit, and 44 did not contribute to either. If the total number of events reported ($539 + 54 = 593$) is increased proportionately to account for the 44 hospitals that did not respond, then the total UK incidence during the 3-month interval might have been 880 (calculated from $(593/91) \times (91 + 44)$). This would extrapolate to 3519 cases per year, giving an incidence of approximately one episode per 17 000 population per annum. This rough approximation does not distinguish between events and patients, but is nevertheless similar to the incidence of one per 15 000 reported from Oxford in 1985[28] and of one in 27 000 reported from Lothian in 1989[29]. A higher incidence has, however, recently been reported from the Gloucester area (one per 6000 per annum), similar to that documented in Finland for the interval 1980–1991 (one per 7000 per annum)[30].

The study provided no epidemiological surprises. The number of men and women was similar, and the median age of 73 years was similar to that of other reports. Occasional studies from the USA describe much younger patients (Blaisdell *et al.*[31] reported a median age of 59 years and Yeager *et al.*[32] a median of 63 years), while some British hospitals deal with older populations (Varty *et al.*[33] reported a median age of 77 years and Singh *et al.*[34] a median of 81 years). Embolism and thrombosis *in situ* were thought to be the cause of acute leg ischaemia in almost equal numbers, together accounting for 78 per cent.

Involvement of a vascular team in the management of all patients with acute leg ischaemia has been a topical issue[23,25] but many hospitals in the UK and Ireland have insufficient vascular surgeons for a formal emergency rota[26,27,35]. A survey of the VSSGBI (regarding ruptured aneurysms) undertaken approximately 9 months after the present audit asked members about vascular on-call rotas; there was an 81 per cent response rate[35]. Only 23 per cent of surgeons provided continuous cover as a contractual commitment, while 67 per cent did so as a professional (non-contractual) understanding. Over 50 per cent of vascular surgeons reported that ruptured aneurysms were dealt with regularly by general surgeons in their hospitals (i.e. no binding vascular rota) or by transfer (rota or *ad hoc*) to other hospitals. Nevertheless, the data presented here provide good evidence that specialist vascular advice and treatment is provided without delay for the vast majority of patients with acute leg ischaemia. It is important also to recognize the part played by vascular radiologists, because more than half of the patients had arteriography in the early stages of management, and 186 then had endovascular treatment.

Publications on the management of acute leg ischaemia tend to reflect the practices of specialist units. Part of the purpose of this study was to see how far management has moved away from the 'old' approach of embolectomy by general surgeons towards the use of arteriography with subsequent thrombolysis, angioplasty and bypass grafting. It is clear that immediate embolectomy still has an important place but this operation is now almost always undertaken by surgeons with a vascular interest. Embolectomy or thrombectomy was also done after initial arteriography in a substantial number of cases. Limb salvage rates after both immediate (73 per cent) and later (81 per cent) thromboembolectomy compare favourably with those of other reports[3,25,28].

Some patients develop acute leg ischaemia as a preterminal event; recognition of these patients and thoughtful conservative treatment represent good medical practice. The association between non-viable limbs and mortality suggests that such patients were managed appropriately (without amputation). Other patients present with unsalvageable legs which are dealt with appropriately by early amputation.

Different management strategies were used selectively for the heterogeneous population of patients in this study and it is therefore not possible to compare the results of different treatments directly. However, similar limb salvage rates were achieved by all the interventional methods: thrombolysis, 69 per cent; angioplasty, 76 per cent; bypass or endarterectomy, 77 per cent; embolectomy, 73–81 per cent. Attempts were made to compare the types of treatment and outcomes of different hospitals, for example those that reported larger *versus* smaller numbers of patients, and teaching hospitals *versus* smaller district general hospitals. However, the relatively small numbers of events from each hospital and the diversity of patients and treatments made meaningful comparisons impossible.

There is great variation in the reported mortality following acute leg ischaemia, but the overall mortality rate of 22 per cent in this study is similar to that of other reports published during the past 10 years[20,24,30,34]. Reports with substantially lower mortality rates are the exception[7]. When making such comparisons it is important to remember that the present study included all patients presenting to hospital with acute leg ischaemia, unlike many others that describe only those having surgical or radiological treatments. With regard to the mortality rate associated with different interventions, it is interesting to note the relatively high rates following endovascular treatment (19 per cent after thrombolysis and 11 per cent after angioplasty) compared with surgical reconstruction (6 per cent). These values suggest that patients having surgery were carefully selected, whereas thrombolysis may have been offered to some patients whose prognosis was more dubious.

The management of acute leg ischaemia has changed radically in recent years; many general surgeons now rightly consider themselves inexperienced to manage the condition. This study shows that almost all patients with acute leg ischaemia across the UK are already being managed by vascular specialists, with frequent use of vascular radiology, and with overall outcomes similar to those published from specialist units. This is being achieved despite insufficient specialists in vascular surgery and radiology for formal or reasonable emergency rotas in most hospitals.

Acknowledgements

The questionnaires for this audit were long and detailed, and the Audit Committee of the VSSGBI recognizes the considerable time and effort taken by members of the Society and other surgeons to report cases. The Committee also acknowledges and thanks the many clinical audit departments whose staff collected data and completed questionnaires.

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Resympathectomy for palmar and axillary hyperhidrosis

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Background The aim was to analyse patterns of failure or symptom recurrence after primary sympathectomy for palmar or axillary hyperhidrosis, and to carry out tactical problem-solving for resympathectomy and review the operative findings.

Methods Over a 2-year period, 20 patients (six men and 14 women) underwent resympathectomy for palmar hyperhidrosis (13 patients, 20 sides) or axillary hyperhidrosis (seven patients, ten sides). T2–3 sympathectomy for palmar hyperhidrosis or T4–5 sympathectomy for axillary hyperhidrosis was performed during the repeat procedure. Criteria for evaluation by means of patient questionnaire included good (more than 80 per cent), fair (50–80 per cent) and poor (less than 50 per cent) improvement.

Results Operative findings included inadequate sympathectomy on 19 sides, nerve regeneration on eight sides and no evidence of previous sympathectomy on three sides. One patient had Kuntz fibre in addition to inadequate sympathectomy. In the palmar hyperhidrosis group, good results were obtained in all 13 patients on all 20 sides after resympathectomy. In the axillary hyperhidrosis group, six of seven patients, or eight of ten sides, showed good results after resympathectomy.

Conclusion The main cause of primary sympathectomy failure was inadequate surgery, and recurrence of palmar or axillary hyperhidrosis was seldom caused by nerve regeneration. The key factor for preventing failed sympathectomy or recurrent palmar or axillary hyperhidrosis is a first-time sympathectomy that is both accurate and adequate. Most patients with recurrent symptoms can be cured by resympathectomy.

Sympathectomy has been performed for more than six decades to treat palmar hyperhidrosis[1], Since the 1980s, dorsal sympathectomy has been gradually replaced by the thoracoscopic approach[2–4]. More than 10 000 thoracoscopic sympathectomy procedures have been reported in Taiwan since 1990[5]. This technique has also been applied to the treatment of axillary hyperhidrosis with acceptable results. The reported primary failure of first-time sympathectomy for palmar hyperhidrosis and recurrence rate is 0–5 per cent[6,7]. Values for axillary hyperhidrosis are not clear. Data from over 1000 thoracoscopic sympathectomies were reviewed; 20 patients with failed sympathectomy or recurrent hyperhidrosis were studied.

Patients and methods

Between January 1995 and July 1997, 20 consecutive patients underwent resympathectomy for either palmar or axillary hyperhidrosis. The patients comprised six men and 14 women aged 15–28 years. Thirteen patients were treated for palmar hyperhidrosis (20 sides) and seven for axillary hyperhidrosis (ten sides). After the primary sympathectomy when the patient's subjective feeling of improvement was only minimal or nil, the procedure was presumed to have failed. Immediate failure after thoracoscopic sympathectomy or return of hyperhidrosis within 1 month was classified as primary failure. Primary failure occurred in 12 patients (18 sides); eight developed recurrent hyperhidrosis (12 sides). The original primary sympathectomy was carried out in the authors' hospital in 12 patients; eight patients had their first operation elsewhere.

The method of reoperation was similar to primary sympathectomy described previously[8,9]. A surface temperature recorder was attached to the distal middle finger for detection of temperature increase after sympathectomy. The sympathetic trunk and ganglion were destroyed by electrocautery. The authors advocate a more extensive nerve destruction in resympathectomy. The extent of sympathectomy in repeat procedures was T2–3 for patients with palmar hyperhidrosis and T4–5 for those with axillary hyperhidrosis.

All patients were followed for at least 9 months after the repeat procedure, either by direct telephone contact or questionnaire.

Results

All operations were accomplished exclusively by thoracoscopy. Operative findings are presented in *Table 1*. Inadequate sympathectomy was defined as evidence of pleural adhesions along the posterior ribs in addition to significant dimpling or scarring of the pleura along the course of the sympathetic trunk. Nerve regeneration was defined when a complete sympathetic trunk could be

Table 1 Operative findings during resympathectomy for palmar or axillary hyperhidrosis

	Palmar ($n = 20$ sides)	Axillary ($n = 10$ sides)
Pleural adhesion	18	10
Inadequate sympathectomy	9	10
Nerve regeneration	8	0
No evidence of previous sympathectomy	3	0
Kuntz nerve fibre	1	0

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traced without significant pleural dimpling or scarring above the sympathetic trunk. Inadequate original sympathectomy was the major cause of primary failure or recurrence of both palmar (nine of 20 sides) and axillary (ten of ten sides) hyperhidrosis.

Repeat sympathectomy was achieved in all patients; a mean temperature increase of 2·7 (range 1·5–4·2)°C was observed. Two patients required chest intubation for significant air leakage; otherwise there were no postoperative complications. Of patients with palmar hyperhidrosis, all 13 (20 sides) had good results (more than 80 per cent improvement). In those with axillary hyperhidrosis, six of seven (or eight of ten sides) showed a good result; the remainder reported 50–80 per cent improvement.

Discussion

The incidence of palmar hyperhidrosis has been reported to be nearly 1 per cent in young Israelis[10]. Since 1990, thoracoscopic sympathectomy has gradually become the mainstream treatment for palmar hyperhidrosis. This technique has also been used to treat axillary hyperhidrosis. Even though the upper extremities receive their sympathetic input from the T2–T6 ganglia, a T2 sympathectomy is usually performed for treatment of palmar hyperhidrosis[11]. However, the lower half of the stellate ganglion[12,13], the T3 ganglion[12] and the Kuntz[14] fibre (present in 10 per cent of the patients) all contribute to the symptoms of palmar hyperhidrosis. This may explain why some patients develop primary failure even after a complete T2 sympathectomy.

In patients demonstrating primary failure, evidence of previous T2 ($n = 8$), T3 ($n = 1$) sympathectomy (in palmar hyperhidrosis) or T3–4 sympathectomy (in axillary hyperhidrosis) could be identified. One patient underwent T3 sympathectomy for palmar hyperhidrosis because the surgeon failed to number the sympathetic ganglion precisely in the primary operation. In one patient with palmar hyperhidrosis, failed sympathectomy may have been caused by the presence of Kuntz fibre. The main cause of recurrent palmar hyperhidrosis was nerve regeneration[4,15]. As in previous reports, all the present patients in this group developed recurrence 3–18 months after the primary operation[4,6]. The operative findings were nerve regeneration (in seven patients with palmar hyperhidrosis) and inadequate sympathectomy (in one patient with axillary hyperhidrosis). The reason for nerve regeneration may be related to incomplete destruction of the sympathetic ganglion. The present experience indicates that inadequate sympathectomy is the main cause of primary failure for both palmar and axillary hyperhidrosis.

In three patients (three sides) no evidence of previous sympathectomy could be identified. In two, owing to proximity of the nerve to the intercostal vessels, the surgeon had left the nerve in place. Using hook or specular type electrocautery, it was possible to manipulate the sympathetic trunk and separate it from the vessels for division and cauterization. In the remaining patient failure of the previous operation was due to diffuse intrapleural adhesions. This patient was also successfully treated after meticulous pneumolysis. Technical difficulties can be overcome by skilled endoscopic techniques.

Because intrapleural adhesions are usually present, a double-lumen endobronchial tube is useful for selective lung ventilation during resympathectomy. The success rate of 20 of 20 sides in patients with palmar hyperhidrosis and eight of ten sides in those with axillary hyperhidrosis after resympathectomy indicates that the strategies followed were effective.

The key factor in preventing primary failure or recurrence of palmar or axillary hyperhidrosis is a primary sympathectomy that is both accurate and adequate. Inadequate sympathectomy is the main reason for primary failure, while nerve regeneration is the main cause of recurrence.

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Controlled prospective study of positron emission tomography using the glucose analogue [^{18}F]fluorodeoxyglucose in the evaluation of pulmonary nodules

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Background Positron emission tomography (PET) is a new imaging technique which, by measuring focal metabolic activities, can make a qualitative statement (benign or malignant) about a tumour. PET has been described in many studies to provide a high diagnostic accuracy for the evaluation of pulmonary coin lesions. However, these studies were not always supported by histological confirmation of the results. In a controlled prospective study, it was investigated whether the diagnostic accuracy of PET is sufficiently high to allow omission of diagnostic thoracotomy or thoracoscopy in the case of a negative finding.

Methods A PET scan was carried out before operation using [^{18}F]fluorodeoxyglucose (FDG) in 50 patients with pulmonary coin lesions (diameter 30 mm or less). All of these lesions were completely removed thoracoscopically or by a formal thoracotomy and were examined histologically. Using the histology results, the diagnostic accuracy of the PET procedure with regard to a benign or malignant diagnosis was evaluated and compared with that of computed tomography (CT).

Results From a total of 54 coin lesions (four of the 50 patients had two lesions) there were 31 malignant (19 primary bronchial carcinomas, 12 metastases) and 23 benign diagnoses. With the PET procedure 28 of 31 malignant and 19 of 23 benign lesions were classified correctly (sensitivity 90 per cent, specificity 83 per cent). False negatives included two bronchial carcinomas and one metastasis. CT had a sensitivity of 100 per cent and specificity of 52 per cent.

Conclusion FDG PET cannot generally be considered as a replacement for diagnostic thoracoscopy or thoracotomy at the present time. However, by combining FDG PET with radiological follow-up, clinical applications may evolve in patients at low risk for a malignant tumour or at high risk for surgical complications.

The evaluation of solitary pulmonary nodules continues to present a diagnostic challenge to oncologists. As a purely descriptive entity, it implies multiple possible diagnoses of widely varying clinical significance.

The prevalence of malignancy among patients with solitary pulmonary nodules in different studies ranges from 20 to 70 per cent[1]. Benign lesions are more common in areas with endemic granulomatous lung disease such as coccidioidomycosis or histoplasmosis. Therefore, North American studies tend to report a lower prevalence of malignant solitary pulmonary nodules than European studies[1,2]. On the other hand,' the probability of malignancy increases with the size of the nodule, and the patient's age and cigarette consumption. Based on European data, the risk of a malignant tumour in a 70-year-old smoker with a 3-cm nodule can be estimated to be as high as 80–90 per cent[1].

Because of the relatively poor diagnostic accuracy of existing imaging techniques[3–9], thoracic surgeons continue to favour early diagnostic thoracotomy[2,10]. The recognized trade-off of this early invasive approach is the relatively high proportion of unnecessary procedures performed to remove what eventually turn out to be benign nodules.

Positron emission tomography (PET) represents a new approach in the attempt to refine non-invasive strategies for the diagnosis of solitary pulmonary nodules. Focal metabolic differences between tumour and surrounding tissue can be imaged effectively using PET. Warburg[11] showed that neoplasms utilize glucose to a greater degree than normal tissue. Lung cancers, in particular, demonstrate this metabolic distinction from normal tissue[12]. [^{18}F]fluorodeoxyglucose (FDG) can be used as a glucose analogue. This substance is taken up by the glucose transporter, phosphorylated, and then remains trapped intracellularly and accumulates within tumour tissue. The radioactive label ^{18}F is a positron emitting isotope. After absorption of their kinetic energy, positrons undergo an annihilation reaction with an electron and two resulting gamma rays of 511 keV are emitted in opposite directions. These gamma rays are sensed by detectors surrounding the patient's body.

Several clinical studies have shown that [^{18}F]FDG PET is useful in the differential diagnosis of solitary pulmonary nodules[13–18], in the staging of bronchial carcinoma[19] and for the detection of recurrent tumours[20]. However, the role of this non-invasive yet costly imaging technique in clinical practice remains to be defined. Therefore, the goal of this study was to analyse prospectively the predictive value of [^{18}F]FDG PET in comparison to other

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diagnostic techniques, especially in comparison to histological results as the gold standard, and to attempt to determine whether PET may be able to replace surgical biopsy

Patients and methods

Between January 1995 and July 1996, 50 patients with pulmonary nodules (diameter 30 mm or less) underwent [^{18}F]FDG PET in addition to standard preoperative diagnostic studies. The patients were aware that surgical removal of the lesion would proceed independently of the results of the PET study. All patients gave written informed consent. The study was approved by the hospital's institutional review board. Patients were asked to participate in the study depending on the availability of PET slots.

The study population consisted of 30 men and 20 women of mean age 59 (range 27–84) years, of whom 46 were diagnosed with a solitary pulmonary nodule and four were found to have two ipsilateral lesions. Two patients with histologically determined bronchial carcinoma were undergoing evaluation of a contralateral nodule. The following preoperative procedures were performed.

Computed tomography

Computed tomography (CT) was performed in-house ($n = 26$) or by external radiologists ($n = 24$). In-house CT was done on a Siemens Somatom Plus scanner (Forchheim, Germany) with spiral option. The imaging protocol included thin-slice (2 mm) spiral scanning of the nodule before and after administration of intravenous contrast agent ($n = 22$) and a contiguous CT study of the whole thorax ($n = 26$). Except for one patient, whose CT study was interpreted by the external radiologist only, CT images were analysed by two operators, and a final diagnosis was made for each nodule in consensus. Criteria for a lesion to be malignant or benign were similar to those described by Siegelman *et al.*[4]. A lesion containing scattered areas of calcification throughout the nodule or a low density focus of fat was considered to be benign. All other lesions were classified as malignant.

Flexible fibreoptic bronchoscopy

Forty-nine patients underwent routine fibreoptic bronchoscopy. Bronchial lavage and brush biopsies were performed in the majority of cases; bronchioalveolar lavage, bronchoscopic biopsy and transbronchial needle biopsy were also performed in selected cases. Histological, cytological and microbiological examinations were performed on all specimens.

[^{18}F]fluorodeoxyglucose positron emission tomography

Data acquisition. Patients fasted for at least 4 h before PET imaging to minimize glucose utilization of normal tissue and to ensure standardized glucose metabolism in all patients. The blood glucose level was measured before the PET examination with blood glucose reagent strips and photometric measurement (Glucometer II, Glucostix; Bayer Diagnostics, Munich, Germany). At the beginning of the scan, the mean(s.d.) blood glucose level was 4·94(1·17) (range 3·89–9·99) mmol/l.

^{18}F was produced with a self-shielded 11-MeV cyclotron (RDS 112; Siemens/CTI (Knoxville, Tennessee, USA) by the acceleration of protons on to an [^{18}O]water target. FDG of high specific activity was produced with a standard technique modified from the synthesis reported by Hamacher et al[21]. Imaging was performed using a whole-body PET scanner (ECAT EXACT; Siemens/CTI, Knoxville, Tennessee, USA).

Patients were injected with 220–370 MBq [^{18}F]FDG. Positioning in the scanner was performed according to the localization of the nodule on the chest radiograph. Forty minutes after tracer injection a static emission scan of 20 min duration was obtained. After the emission scan, a transmission scan with ^{68}Ge rod sources was performed for 15 min to yield approximately 4 million counts per slice. Emission data corrected for randoms, dead time and attenuation were reconstructed by filtered back-projection (Hanning filter with cut-off frequency 0·4 cycles/bin). The resulting in-plane image resolution of transaxial images was approximately 8 mm full-width-half-maximum (FWHM), with an axial resolution of approximately 5 mm FWHM.

Image analysis. Qualitative and quantitative image analysis was performed before surgery in all patients. Attenuation-corrected images were normalized for injected dose and body mass resulting in parametric images that represented regional standardized uptake values (SUVs)[22], where SUV = (tissue concentration (Bq/g))/(injected dose (Bq)/body mass (g)). SUV-normalized images were analysed on the console of the ECAT scanner using a linear grey scale with SUV values ranging from 0 to 5.

Quantitative analysis. The maximum SUV (SUVmax) of all lesions with focal FDG uptake was determined. For lesions that could not be identified by increased FDG uptake, a region of interest (ROI) was placed according to the location of the nodule in the transmission scan or the chest radiograph and the SUVmax within this ROI was used.

Partial volume effects can lead to a considerable underestimation of the true activity concentration within lesions with a diameter less than twice the resolution of the PET scanner at FWHM[23]. As many tumours in the present study were below this limit, a previously described partial volume correction was applied for all lesions with focally increased FDG uptake[24,25]. Briefly, this method determines the size of a lesion in the emission scan and multiplies the measured activity concentration by a corresponding correction factor.

Qualitative evaluation. PET images were analysed by two observers (W.A.W. and W.R.) without information on the patient's clinical history or previous technical examinations except the chest radiograph. Based on the results of a pilot study, a lesion with a SUVmax of 2·5 or more was considered to be malignant[26]. In addition to this quantitative parameter, the pattern of FDG uptake in the lesion was used for the classification. Small but definitively circumscribed focal abnormalities were considered as malignant, even when the SUVmax was below 2·5. On the other hand, diffusely increased FDG uptake was classified as benign even when the SUVmax was above 2·5. For all patients, a written final PET diagnosis was made before operation.

Surgical procedure

After the preoperative examinations, all patients subsequently underwent complete surgical excision of the nodules, performed by or assisted by one experienced operator. The tissue obtained was sent for histological analysis.

Statistical analysis

Sensitivity, specificity and positive and negative predictive values of the diagnostic tests were calculated using standard formulas. In addition, 95 per cent confidence intervals for these parameters were calculated by use of the F-distribution[27]. All statistical tests were performed at the 5 per cent level of significance. For evaluation of the difference between SUV values in benign and malignant lesions, the Mann–Whitney U test was used. The ability of quantitative parameters to differentiate between benign and malignant lesions was analysed by calculation of receiver operating characteristic (ROC) curves for partial volume-corrected and uncorrected SUV values. A modified t test was used to determine whether there was a significant difference between the area under the ROC curves (CLABROC program; C. E. Metz, University of Chicago, Chicago, Illinois, USA[28]).

Results

The mean(s.d.) diameter of the excised lesions was determined radiographically to be 18(7) (range 3–30) mm. In selected cases, the specimen diameter measured after excision differed from the size determined previously. One bronchioloalveolar carcinoma, which on CT appeared to be a discrete nodule 2 cm in diameter, proved to have star-shaped extensions, with a subsequent maximal diameter of 6 cm. All excision biopsies were performed with the assistance of frozen-section analysis performed for suspected tumours. For proven bronchial carcinomas, standard lobectomy with lymph node excision was subsequently performed. Specifically, 18 patients underwent lobectomy, 27 underwent wedge resection (video-assisted thoracoscopic wedge resection in some cases), eight underwent enucleation and one had a segmentectomy. There were no perioperative deaths (within 30 days).

Histological findings

There were 31 malignant tumours (19 primary bronchial carcinomas and 12 metastases) and 23 benign nodules. Adenocarcinoma was the most common bronchial carcinoma (15 of 19 cases). Tumour node metastasis (TNM) staging was as follows: $T_1 N_0$ (six), $T_1 N_1$ (one), $T_1 N_x$ (one), $T_2 N_0$ (eight), $T_2 N_1$ (one) and $T_2 N_x$ (two). Individual histological diagnoses are shown in *Tables 1* and *2*. Of the four patients with two nodules, the following combination diagnoses were found: (1) two metastases (colon carcinoma), (2) two leiomyomatous hamartomas, (3) one chondrohamartoma and scar tissue, and (4) one metastasis (rectal carcinoma) and one anthracotic lymph node. Of the two patients with known bronchial carcinoma and a contralateral nodule, one had a chondrohamartoma and one a tuberculoma.

Table 1 Histological findings and numbers of correct positron emission tomography diagnosis (true positive) in malignant lung tumours ($n = 31$)

Histology	No. of patients	Correct PET diagnosis
Lung cancer	19	17
Adenocarcinoma	15	14
Squamous cell	2	2
Neuroendocrine	1	0
Adenoidcystic	1	1
Metastatic lesions	12	11
Colon	6	6
Renal	2	2
Breast	1	1
Thyroid	1	0
Bladder	1	1
Non-Hodgkin's lymphoma	1	1

PET, positron emission tomography

Table 2 Histological findings and correct positron emission tomography diagnosis (true negative) in benign lung tumours ($n = 23$)

Histology	No. of patients	Correct PET diagnosis
Chondrohamartoma	12	10
Leiomyomatous hamartoma	2	2
Tuberculoma	2	0
Scar tissue	2	2
Anthracotic lymph node	2	2
Interstitial fibrosis	1	1
Bronchogenic cyst	1	1
Sclerosing haemangioma	1	1

PET, positron emission tomography

Bronchoscopy

Of the 49 patients studied (two with outside procedures), bronchoscopy showed bronchial carcinoma by cytology in two cases (one adenocarcinoma and one neuroendocrine carcinoma) and tuberculoma by microbiology in one case. No definitive diagnosis was possible in the remainder.

Positron emission tomography

Twenty-eight of 31 malignant nodules and 19 of 23 benign lesions were diagnosed correctly by qualitative image interpretation according to the above criteria. Two chondrohamartomas and two tuberculomas were incorrectly interpreted as malignancies; one adenocarcinoma, one neuroendocrine carcinoma and one metastatic thyroid carcinoma were given a false-negative diagnosis as benign lesions. Thus, the sensitivity using qualitative image interpretation was 90 (95 per cent confidence interval 74–98) per cent, with a specificity of 83 (61–95) per cent. The positive predictive value was 88 (71–96) per cent; the negative predictive value was 86 (65–97) per cent). Overall, accuracy was 87 (76–95) per cent. *Fig. 1* shows an example of a typical positive FDG PET study of an adenocarcinoma.

Mean(s.d.) SUVmax in malignant lesions was 3·85(2·24), and was significantly higher ($P <$ 0·0001) than that in benign lesions (1·48(0·77)). By correction of the partial volume effect, the SUV of malignant tumours increased to 5·06(2·89) and that of benign lesions increased to 1·55(0·91) ($P <$ 0·0001) (*Fig. 2*). ROC analysis showed a slight advantage for the partial volume-corrected SUV compared with the uncorrected SUV (*Fig. 3*). However, this difference was not statistically significant. Using a cut-off value of 2·0 for SUVmax, a sensitivity of 90 (74–98) per cent and a specificity of 87 (59–98) per cent were achieved. For partial volume-corrected SUVs, the optimal cut-off value was 2·3. This cut-off value resulted in a sensitivity of 94 (79–99) per cent with a corresponding specificity of 80 (52–96) per cent.

Computed tomography

CT correctly identified all malignant tumours (sensitivity 100 (89–100) per cent). However, 11 benign lesions were erroneously classified as malignant resulting in a low specificity of 52 (31–73) per cent. Accuracy was 80 (66–89) per cent, positive predictive value 74 (58–86) per cent and negative predictive value 100 (74–100) per cent. There was no difference in sensitivity or specificity between internal and external CT.

Discussion

The diagnostic investigation of solitary pulmonary nodules comprises of several invasive and non-invasive diagnostic techniques. The results of fibreoptic bronchoscopy are especially disappointing for small, peripheral and matous polyposis where an adenocarcinoma has also been reported in the anal canal[22].

Attempts to introduce new terms to an operation where there is already a plethora of terminology are rightly met with resistance. However, in double-stapled restorative proctocolectomy, recognition that a cuff of diseased columnar mucosa has been retained is an important concept. This epithelium can usefully and accurately be termed the 'columnar cuff' and the present authors propose the introduction and wider use of this term[5]. The columnar cuff is defined as the retained columnar epithelium between the upper border of the ATZ below, and the pouch–anal anastomosis above. The acknowledgement of a retained 1·5–2·0-cm columnar cuff of diseased mucosa is important for follow-up after restorative proctocolectomy.

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Anal endosonography in patients with anorectal symptoms after haemorrhoidectomy

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Background Anorectal symptoms after haemorrhoidectomy are common and treatment is often empirical. Because of this, an audit was carried out of the value of anal endosonography in patients with anorectal symptoms after haemorrhoidectomy.

Methods Between May 1993 and February 1997, 16 patients (ten men and six women of median age 56 (range 35–77) years) were investigated by anal endosonography for anorectal symptoms after haemorrhoidectomy which involved anorectal incontinence ($n = 10$), anal pain ($n = 4$) and obstructive defaecation ($n = 2$). The findings were compared with those in a matched group of asymptomatic patients after haemorroidectomy.

Results Anal endosonography demonstrated an abnormality in 12 symptomatic patients. Of the ten patients with anorectal incontinence, endosonography showed an internal anal sphincter defect ($n = 5$), a combined sphincter defect ($n = 2$) and an isolated external anal sphincter defect ($n = 1$). Normal appearances were seen in all asymptomatic patients. The endosonographic abnormalities of the four patients with anal pain included internal anal sphincter defect ($n = 1$), extrinsic mass ($n = 1$), and intersphincteric abscess ($n = 1$). One of the two patients with obstructive defaecation had an isolated external anal sphincter defect on endosonography.

Conclusion These results show a high yield of endosonographic abnormalities in patients who experience symptoms after haemorrhoidectomy. In particular, occult sphincter injury as a cause of incontinence in these patients can frequently be demonstrated.

Haemorrhoidectomy is a common procedure associated with few postoperative problems. However, these can be significant, especially that of anorectal incontinence. Evaluation of these patients can be difficult and treatment often remains empirical. The advent of anal endosonography has been a significant advance in the investigation of anorectal pathology. It has been shown to be not only accurate in demonstrating the normal anatomy[1], particularly of the internal anal sphincter (IAS), but is also of proven value in the investigation of anorectal incontinence[2] and pathology in the intersphincteric space.

However, little has been written about the role of endosonography in patients with anorectal symptoms after haemorrhoidectomy. The purpose of the present study was to assess the prevalence of endosonographic anal abnormalities in patients with anorectal symptoms after haemorrhoidectomy.

Patients and methods

Between May 1993 and February 1997, 16 patients (ten men and six women of median age 56 (range 35–77) years) were referred to the authors' tertiary coloproctology specialist unit from other surgical centres in South Wales after they developed symptoms following haemorrhoidectomy. The referring centres did not carry out anal endosonography routinely before haemorrhoidectomy. None of these patients originated from the authors' unit. The median interval between haemorrhoidectomy and presentation to the unit was 6 months (range from 1 month to 30 years). Ten of the 16 patients had anorectal incontinence (median Cleveland Clinic score 12 (range 8–18)[3]). Of the ten patients with incontinence, seven complained mainly of mucus leakage, seepage and flatus incontinence, and three suffered from urge incontinence as well. Four further patients suffered from long-standing intractable anal pain after haemorrhoidectomy and the remaining two had symptoms of obstructive defaecation.

All patients were assessed clinically and underwent anal endosonography. They were all examined in the left lateral position by one examiner (B.P.) using a Bruel and Kjër type 1850 scanner (Bristol, UK), with a 7·5-MHz (more recently a 10-MHz) rotating transducer covered with a hard sonolucent plastic cone with an outside diameter of 17 mm. The anal canal was assessed at superficial, mid and deep levels.

Endosonographic appearances in the study group were compared with those in a control group of 16 patients (ten men and six women of median age 58 (range 40–80) years) who had undergone haemorrhoidectomy on the authors' unit and who were asymptomatic at a median follow-up of 3 months after operation.

Results

Study group

Twelve of the 16 symptomatic patients had lesions demonstrated on anal endosonography. These can be conveniently divided into three groups.

Patients with incontinence. Of the ten patients with anorectal incontinence, seven had disruption of either the IAS ($n = 5$) or both sphincters ($n = 2$) without predisposing cause other than the operation (*Fig. 1*). These defects corresponded to the sites of haemorrhoidectomy. One patient had features of an isolated external anal sphincter (EAS) injury which was located anterolaterally on the

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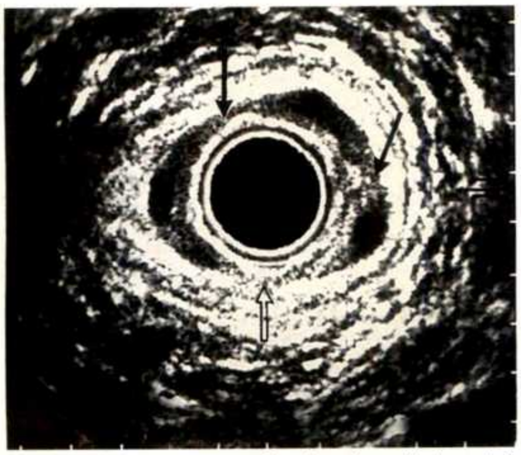

Fig. 1 Endoanal ultrasonogram showing three distinct defects (open arrow) and thinning (closed arrows) of the internal anal sphincter corresponding to the sites of haemorrhoidectomy. (Left: posterior; right: anterior; top: right lateral; bottom: left lateral)

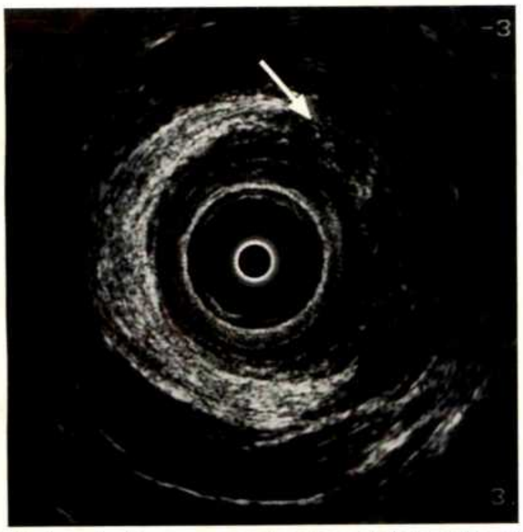

Fig. 2 Endoanal ultrasonogram showing a defect in the external anal sphincter in the anterolateral position on the right side (arrow) in a patient who had undergone vaginal delivery. (Orientation as for *Fig. 1*)

right (*Fig. 2*) and two had a normal endosonogram. None of these patients was incontinent before haemorrhoidectomy.

Patients with anal pain. Four patients had anal pain at a median follow-up of 15 months (range from 1 month to 30 years) after operation. Endosonographic findings included IAS injury ($n = 1$), extrinsic mass ($n = 1$) (*Fig. 3*), intersphincteric abscess ($n = 1$) and normal appearance ($n = 1$).

Patients with obstructive defaecation. Of the two patients with obstructive defaecation after haemorrhoidectomy in this series, one demonstrated an isolated EAS defect on endosonography and the other was normal.

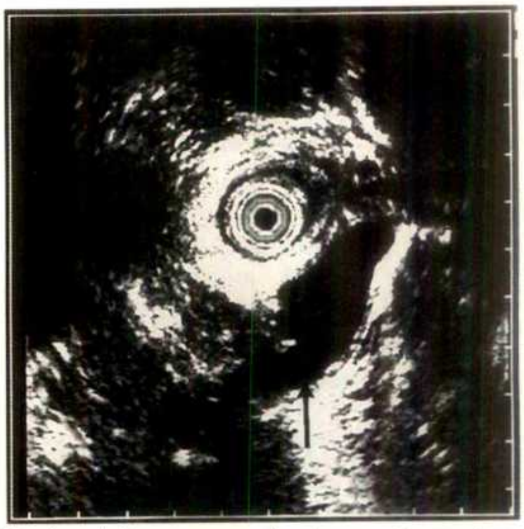

Fig. 3 Endoanal ultrasonogram showing a cystic area (arrow) separate from and outside the anal sphincter complex in a patient who presented with anal pain. This was thought to represent an abscess, but proved to be a benign cystic tumour on magnetic resonance imaging. (Orientation as for *Fig. 1*)

Historical controls

Endosonographic appearances were normal in all control patients who had undergone haemorrhoidectomy and who did not have symptoms after operation.

Discussion

The present study may be criticized on the grounds that anal endosonography was not carried out before haemorrhoidectomy. Hence, the morphology of the anal sphincter complex before surgery remains unknown. Nevertheless, 12 of the 16 patients in this study exhibited lesions on endosonography and nine of these corresponded to the sites of haemorrhoidectomy. Moreover, in three of these cases, the lesions were at multiple sites. In contrast, the asymptomatic patients had normal anal sphincter appearances.

In the symptomatic patients, injudicious haemorrhoidectomy seems the most likely cause of injury to either or both sphincters. In two other patients, anal endosonography revealed isolated defects in the EAS anterolaterally on the right side of the sphincter complex. Only one of these patients presented with anorectal incontinence. Both patients were women and had undergone vaginal delivery. As suggested by Felt-Bersma *et al.*[4], obstetric trauma would seem to be a more likely cause than haemorrhoidectomy for the presence of sphincter injury in these two patients. The remaining two patients had lesions that were probably unrelated to haemorrhoidectomy.

The findings from this report are in keeping with those of similarly designed studies[4,5] which have employed anal endosonography to examine the anatomy of the anal sphincter complex after anal surgery. Felt-Bersma *et al.*[4] performed endosonography on 50 patients who had undergone previous anal surgery and 24 of these had been subjected to haemorrhoidectomy. They found occult sphincter defects in three of the patients. Nielsen *et al.*[5] examined nine patients with anorectal incontinence after anal dilatation, haemorrhoidectomy and drainage of anal abscess. These authors demonstrated injury to the IAS in five patients, to the EAS in two and to both sphincters in two cases. In contrast to other studies, the present series demonstrates that causes other than sphincter disruption may account for symptoms after haemorrhoidectomy, as evidenced by the observation of chronic intersphincteric abscess in one patient and an extrasphincteric mass in another.

Not all patients with sphincter disruptions after anal surgery experience incontinence in the immediate postoperative period[4]. Nevertheless, Felt-Bersma has emphasized that detection of these lesions is important because patients may be at risk of developing incontinence in later life as anal pressures, rectal compliance[6–8] and pudendal nerve function[9] decrease with age. Notwithstanding these observations, anorectal incontinence is an uncommon but well recognized immediate sequel of haemorrhoidectomy. It has been postulated that the failure to create proper tissue planes may result in injury to either sphincter[4,10,11]. The findings from the present study in which seven of ten patients with anorectal incontinence had sustained injury to one or both sphincters support these observations. Moreover the type of incontinence in the subgroup of patients with isolated IAS defects consisted mainly of mucus leakage, seepage and flatus incontinence, whereas those with combined IAS and EAS defects had a significant degree of urge incontinence. Thus, from a clinical standpoint, the type of incontinence correlated with the defects visualized on anal endosonography. The cause of incontinence in patients with normal anal endosonography or a previous obstetric tear remains conjectural, but may be related to removal of anal cushions[12–14].

Anal pain in the immediate perioperative period after haemorrhoidectomy remains a vexing problem. Less is known about longer-term postoperative discomfort. The findings from the present endosonographic study indicate that alternative anal pathology may exist, such as an extrinsic mass or an intersphincteric abscess; this may draw into question the original cause of symptoms. It is, however, difficult to explain the cause of pain in the patient with the normal anal endosonography and in the patient with an isolated IAS defect.

In conclusion, the findings from the present study are significant enough to warrant further evaluation of the role of anal endosonography in the investigation of patients with symptoms after haemorrhoidectomy.

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Short note

Pouch perineal rectosigmoidectomy gives better functional results than conventional rectosigmoidectomy in elderly patients with rectal prolapse

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Abdominal rectopexy with or without resection has become the operation of choice for rectal prolapse because of a low recurrence rate, but it is a major operation for elderly, infirm patients with a short life expectancy[1]. In this group, a perineal procedure is often preferred using either the Délorme's operation[2] or rectosigmoidectomy[3], but recurrence rates are variable and can be high[4,5].

Patients and methods

Patients with full-thickness rectal prolapse, aged over 80 years or with comorbidity in whom an abdominal approach was contraindicated, were treated by rectosigmoidectomy either with a colonic pouch or, as in the conventional procedure with a straight coloanal anastomosis. This non-randomized comparison involved all such patients treated between January 1993 and December 1996. The study was approved by the local research ethics committee. The normally distributed data are recorded as mean(s.d.) and the χ^2 test was used for analysis of the functional scores[6].

Pouch perineal rectosigmoidectomy (PPRS) involved everting the prolapse. The rectal wall was divided 1 cm from the dentate line so as to retain the anal transitional zone. The posterior dissection involved dividing Waldeyer's fascia to identify the levators and the mesorectum, which was dissected from the presacral fascia. The anterior plane was developed between the rectum and the posterior vaginal wall to the level of the rectovaginal pouch. The attenuated lateral ligaments and the mesorectum were divided and the entire rectum was delivered onto the perineum. None of the sigmoid vascular arcades was divided until the sigmoid colon had been mobilized and the proposed transection line determined to produce an 8 × 8-cm pouch. Only then were the sigmoid vessels divided and the colon transected with a linear staple cutter. The divided bowel was folded back adjacent to the proximal colon using stay sutures to facilitate a side-to-side stapled anastomosis through the apex of the colonic pouch. Before constructing the pouch, three rectopexy sutures were inserted between the presacral fascia at the level of S3 and the divided colon. The pouch was then constructed with a linear staple cutter through the apical enterotomy; the pelvic floor muscles were repaired in anterior and posterior directions with interrupted 2/0 polypropylene sutures but these were not tied until the rectopexy sutures secured the divided colon against the sacral promontory. Furthermore, the pelvic floor repair sutures were only tied after inserting a finger through the colonic pouch to ensure that the pelvic floor repair was not too tight. A standard coloanal anastomosis then completed the operation with interrupted 2/0 polyglycolic acid sutures.

Conventional rectosigmoidectomy involved continuing the excision beyond the rectum by serially dividing the sigmoid vessels until all the available colon could be delivered onto the perineum. This often involved 20-30 cm of bowel. The colon was therefore straight when constructing the coloanal anastomosis, so a rectopexy was neither feasible nor considered necessary.

Results

Fourteen patients underwent rectosigmoidectomy during the 4 years of the study; seven underwent PPRS (mean age 82 (range 74-86) years; one man) and seven underwent conventional perineal rectosigmoidectomy (PRS) (mean age 76 (range 66-81) years; all women). The mean(s.d.) hospital stay was 11·7(4·9) days for PPRS compared with 8·9(2·6) for PRS. One patient developed a leak from the pouch after PPRS which caused local sepsis; this necessitated laparotomy, pouch excision and a new coloanal anastomosis with a covering loop ileostomy, which has been successfully closed. There was no recurrence of the prolapse after PPRS although one patient had mild mucosal prolapse. In comparison, three patients had a recurrent prolapse after PRS, all of whom have undergone successful resection rectopexy. The changes in bowel function before and after operation are shown in *Table 1*. Only PPRS was associated with improvement in symptoms. Using the Cleveland Clinic score[6], there was a significant overall improvement after PPRS (11·0(7·4) to 3·6(4·6); $P < 0·05$) whereas there was no change after PRS (7·8(5·5) to 7·2(4·8); P not significant). Significant improvement was also recorded for continence to liquid and flatus after PPRS ($P < 0·02$ and $P < 0·01$ respectively) but no improvement was reported with PRS. In this elderly population, many of whom were domiciled in nursing homes, postoperative physiological assessment was incomplete (data available for only five of 14 patients).

Discussion

These results suggest that PRS is associated with a higher recurrence rate than abdominal resection rectopexy even when adjuvant pelvic floor repair was used; these poor

Table 1 Functional results

	Pouch ($n = 7$)		No pouch ($n = 7$)	
	Before operation	After operaton	Before operation	After operation
Incontinence	6	2	6	6
Urgency	5	3	6	6
Soiling	6	2	6	6
Constipation	1	2	0	0
Poor evacuation	1	1	2	1
Bowel habit (times per day)*	2·5(1·0)	2·1(1·3)	2·2(0·8)	2·0(0·7)

*Values are mean(s.d.)

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results are not unique[7]. The poor functional results after PRS, particularly with respect to incontinence, urgency and soiling, are almost certainly related to loss of reservoir capacity due to a rather narrow colon above the anal anastomosis, together with some reduction in anal sphincter function[8]. In contrast, PPRS was not associated with recurrent prolapse probably because rectopexy sutures were used to fix the transected colon against the presacral fascia. Furthermore, construction of a pouch improved the symptoms of urgency and soiling with relief of incontinence in two of six patients.

Perhaps the most worrying feature of this experience is the single patient who developed an ischaemic leak from a colonic pouch. Colonic ischaemia in this operation is a real hazard unless great care is taken to preserve the sigmoid arcades to the retained sigmoid colon. Clearly, if a major ischaemic leak develops, further surgery is mandatory and will usually necessitate pouch excision and the risk of a permanent stoma. On the other hand, conventional rectosigmoidectomy is not without its complications as, like others[9], three of seven patients in this study developed a recurrent full-thickness rectal prolapse, despite extensive colorectal resection and concomitant pelvic floor repair. If patients are dissatisfied with the recurrent prolapse, as was the case with the present three patients, they too face a major abdominal operation which could conceivably be avoided by PPRS.

The majority of patients with a full-thickness rectal prolapse are best managed by abdominal resection rectopexy[1]. However, there is a small group of patients who are extremely old or who have comorbidity, in whom an abdominal procedure will be contraindicated and control of the prolapse is feasible only by a perineal procedure. One alternative is the Délorme's procedure, which carries a low morbidity but is associated with a rather high recurrence rate[10]. It would be of value to compare these two options in the same group of high-risk patients. Nevertheless, these data certainly seem to indicate that PPRS offers substantial advantages over PRS in patients at high risk who require a perineal operation.

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Rectal adaptation to distension in patients with overt rectal prolapse

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Background High recovery rates of continence are observed after surgical procedures for rectal prolapse. Increases in rectal compliance but no obvious rise in anal pressures have been reported. The authors' hypothesis was that decreased rectal adaptation to distension may contribute to incontinence in patients suffering from overt rectal prolapse.

Methods This was a prospective study conducted in 20 consecutive incontinent patients suffering from overt rectal prolapse with no mucosal change (two men and 18 women; mean(s.e.m.) age 50(3) years). They were compared with 20 age- and sex-matched patients with incontinence without rectal prolapse and ten age- and sex-matched healthy volunteers observed during the same period. The subjects were submitted to phasic isobaric distension of the rectum with an electronic barostat. Anal pressures, perception scores and rectal volumes were recorded at six different preselected pressures.

Results Compared with healthy subjects, maximum rectal volumes (mean(s.e.m) 98(6) *versus* 167(11) ml; $P = 0.005$), volumes related to compliance (56(5) *versus* 100(9) ml; $P = 0.004$) and tone (41(3) *versus* 67(4) ml; $P = 0.003$) were decreased significantly in the rectal prolapse group. Prolapse and incontinence groups did not differ significantly with respect to rectal adaptation for all three parameters and steps of distension considered.

Conclusion Patients suffering from overt rectal prolapse had markedly impaired rectal adaptation to distension which may contribute to incontinence.

Faecal incontinence occurs in 25–78 per cent of patients suffering from overt rectal prolapse[1–9]. Weak anal function for both resting and squeezing tests is frequently reported but its relationship to this symptom remains questionable and the mechanism of recovery of continence after surgical procedures is debated[10–16]. In abdominal surgical series without a surgical procedure on the anal sphincters, reported continence recovery rates vary between 30 and 88 per cent[1,3,5,7–9,17–21]. Interestingly, continence is restored although there is no evidence for obvious[10,11,15,22] or small[9,13,23] rises of both resting and squeeze anal pressures. Continence improvement may also occur in patients with very poor sphincter function[9,13,23]. It has been postulated that incontinence may result from a profound internal sphincter inhibition subsequent to high rectal pressure waves induced by the prolapse itself[13,14,24]. Another explanation may be an impairment of rectal adaptation to filling, related to wall fibrosis or autonomic neuropathy. The present study tested this hypothesis by comparing a consecutive group of patients suffering from overt rectal prolapse with age- and sex-matched healthy subjects and incontinent patients without rectal prolapse.

Patients and methods

Study groups

Between June 1995 and May 1997, 20 consecutive patients (18 women; mean(s.e.m.) age 50(3) years) suffering from overt rectal prolapse and symptoms of faecal incontinence to liquid and/or solid stool were enrolled. They were compared with 20 age- and sex-matched incontinent patients without rectal prolapse (18 women; mean age 50(3) years), observed during the same study period, and with ten age- and sex-matched healthy volunteers (nine women; mean age 51(4) years). Patients were excluded if they were pregnant, had been treated by medication containing cholinergic agents, α-adrenergic drugs and cathartic laxatives during the previous 6 months, or had undergone pelvic radiation, perineal or anal sphincter reconstruction or a surgical procedure on the rectum. Patients were also excluded when the following abnormalities were encountered: chronic diarrhoea, encopresis or stool impaction, severe constipation, rectal or colonic mucosal changes, suspected or proven neurological abnormalities, psychiatric disorders and diabetes. High-grade prolapse (apparent on straining) was an exclusion criterion in the incontinence group. Healthy volunteers were free from gastrointestinal symptoms or a surgical past history affecting the pelvis.

Each patient underwent standard questionnaire, physical examination, anal endosonography, defaecating proctography and anal manometry. The questionnaire focused on main anorectal complaints, and surgical and obstetric past histories. Continence failure within the previous month was scored on the basis of a 0–18-point scale[25]. Anal endosonography (EUM 20; Olympus Scop Médecine, Rungis, France) identified defects involving external and internal sphincters. Defaecating proctography was performed as described previously to identify high-grade prolapse, perineal descent and rectocele, and to analyse rectal emptying[26]. High-grade prolapse was defined by an intra-anal or exteriorized intussusception of the rectal wall at strain. Perineal descent was quantified by the maximal length which separated the upper anal canal site and the pubococcygeal line during defaecation. Anal manometry was performed using a three-lumen water-perfused catheter assembly to record mean maximum resting and mean squeeze pressures at both upper and lower parts of the anal canal.

Study design

Each patient was submitted to one session of phasic isobaric distension of the rectum. Studies on rectal isobaric distension in

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incontinent and healthy subjects had been reviewed previously and approved by the ethics committee of this institution (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Hôtel-Dieu, Rennes, France).

Equipment and parameters investigated

An electronic barostat was used to stimulate the rectum and anal manometry was used to evaluate responses at different levels of the anal canal. Distension procedures were performed with a highly compliant polyethylene bag placed within the rectum and connected to an electronic barostat (ABS, Saint Dié, France) as described previously elsewhere[27]. Anal canal pressures were monitored using a three-lumen water-perfused catheter (R3B and PIP4–4; Mui Scientific, Mississauga, Ontario, Canada) assembly with radially distributed side holes, spaced 0·5 cm apart for the two proximal holes. Anal pressures were recorded firstly during resting and voluntary squeezing states. During isobaric distension of the rectum, rectal and anal pressures were recorded continuously by a computerized motility system (Smartlab Computerised Motility System; Solal-Sandhill, Strasbourg, France).

Phasic distension was performed by rapidly inflating the bag to successive predetermined ascending levels of pressure (increment 5 mmHg), each level being maintained for 60 s and separated from the next by a 60-s rest period at 0 mmHg. The same pressure limits were fixed during the whole study protocol (6–31 mmHg).

In response to the rectal distension protocol, the following parameters were monitored.

Anal pressures in the upper and lower anal canal. Conventionally, the upper part is thought to reflect the manometric activity of the internal anal sphincter and the lower part the activity of the external anal sphincter. At each pressure step, the anal pressure was expressed as the mean pressure recorded at the level investigated.

Maximum rectal pressure and motility index. Maximum rectal pressure and motility index was recorded by the manometric device during each plateau pressure in order to analyse the occurrence of rectal contractions. The mathematical computation of motility indices was the product of the mean rectal pressure and the period of recording activity[28].

Maximum volume of the rectum. Maximum rectal volume was recorded at the end of each step of preselected pressure.

Volume related to compliance. This is defined by a volume variation in response to an ascending pressure. It represents the difference between the resting state (0 ml) and the measured volume when the preselected pressure is just reached. Because this is a volume variation over the variation of two levels of pressure, this phase may reflect rectal compliance.

Volume related to tone. This is a volume variation in response to a stabilized preselected pressure (maximum volume – initial volume). It describes rectal tone (pressure variation 0 mmHg) in this phasic isobaric distension model.

Sensation intensity. Sensation intensity was assessed at each pressure step (when rectal pressure was just stabilized), using a six-point scale ranging from no sensation to pain[29].

Statistical analysis

Quantitative variables were expressed as mean(s.e.m.) and the percentage variation between groups was calculated. Distributions of qualitative variables were compared between groups with the χ^2 test; distributions of quantitative parameters were compared between groups by means of analysis of variance and unpaired *t* tests. For each type of distension, two-way (group, pressure step) analyses of variance were performed on anal and rectal pressures, rectal volumes and perception scores. $P < 0·05$ was considered to be statistically significant.

Results

Population

Table 1 presents the general characteristics of the study population. The two groups of patients did not differ with respect to parity, weekly stool frequency, incontinence score and surgical past history. *Table 2* shows that rectoperineal disorders were similar between groups of patients, except for a more pronounced perineal descent during straining efforts in the rectal prolapse group. As assessed by objective tests, the magnitude of incontinence and dyschezia was similar between groups and sphincter defects occurred similarly in both groups. *Table 3* presents data obtained using routine anal manometry. As expected, both anal and squeeze pressures were lower in patient groups than in healthy subjects. Moreover, compared with values in those with faecal incontinence, mean squeeze and mean resting pressures at the upper and lower part of the anal canal were significantly lower in patients with rectal prolapse.

Manometric recordings

Pressure steps of distension significantly modified manometric recordings in the rectum and upper anal canal ($P < 0·001$ for all parameters, two-way repeated-measures analysis of variance). Such an effect was not encountered in the lower part of the anal canal ($P = 0·64$). Higher rectal distensions decreased anal pressures at the upper part of the anal canal and they increased both

Table 1 General characteristics of the study groups

	Prolapse ($n = 20$)	Incontinence ($n = 20$)	Healthy ($n = 10$)
Age (years)*	50(3)	50(3)	51(4)
Sex ratio (M:F)*	2:18	2:18	1:9
Parity*	1·4(0·4)	2·4(0·4)	2·1(0·3)
Weekly stool frequency*	8·3(1·4)	11·4(1·4)	6·8(0·9)
Incontinence score (0–18)*	11·3(1·3)†	12·4(0·9)	0
No. with previous surgery	10	14	3

*Values are mean(s.e.m.). †$P = 0·001$ *versus* healthy (Student's *t* test)

Table 2 Main disorders encountered at evacuation proctography and anal endosonography

	Prolapse ($n = 20$)	Incontinence ($n = 20$)
Perineal descent (mm)*	71(4)	57(4)‡
Rectocele†	7	6
Complete rectal emptying†	14	11
Emptying duration (s)*	27(4)	30(4)
Barium paste leakage < 300 ml†	7	11
First volume leakage (ml)*	136(21)	142(15)
EAS defect†	6	11
IAS defect†	13	11

Values are *mean(s.e.m.) or †number of patients. EAS, external anal sphincter; IAS, internal anal sphincter. ‡$P = 0·012$ *versus* prolapse group (Student's *t* test)

Table 3 Basal and squeeze pressures at routine anal manometry

					P*		
Anal canal	Prolapse ($n = 20$)	Incontinence ($n = 20$)	Healthy ($n = 10$)	Variance (all groups)	Prolapse *versus* incontinence	Prolapse *versus* healthy	Incontinence *versus* healthy
Upper part							
Mean resting pressure	20(2)	34(4)	69(9)	665	0·010	0·001	0·001
Lower part							
Mean resting pressure	22(3)	35(5)	66(7)	654	0·036	0·001	0·002
Maximum squeeze pressure	64(7)	90(11)	172(17)	3402	0·057	0·001	0·001
Mean squeeze pressure	39(3)	66(8)	11(9)	1564	0·003	0·001	0·001

Values are mean(s.e.m.). Analysis of variance showed $P < 0{\cdot}001$ for all measurements. *Student's t test

maximum rectal pressures and motility indices. Maximum rectal pressures and rectal motility indices did not differ between groups ($P = 0{\cdot}62$ and $P = 0{\cdot}95$ respectively) for all pressure steps of distension (no significant pressure × group interaction; $P = 0{\cdot}57$ and $P = 0{\cdot}56$ respectively). *Fig. 1* shows anal responses to rectal isobaric distension according to the pressure step of distension and the study group. A group effect was observed at the upper and lower levels of anal recordings, but it depended on the pressure step of distension at the upper part only (pressure × group interaction; $P < 0{\cdot}001$ and $P = 0{\cdot}97$ respectively). Compared with healthy subjects, anal pressures were significantly decreased at both upper (mean −47 per cent) and lower (mean −61 per cent) parts of the anal canal in the prolapse group ($P = 0{\cdot}003$). For all steps of rectal distension, anal pressures in the upper anal canal were lower in the rectal prolapse than in the incontinence group (mean −37 per cent) ($P = 0{\cdot}032$). In contrast, anal pressures in the lower anal canal were similar in these two groups ($P = 0{\cdot}14$).

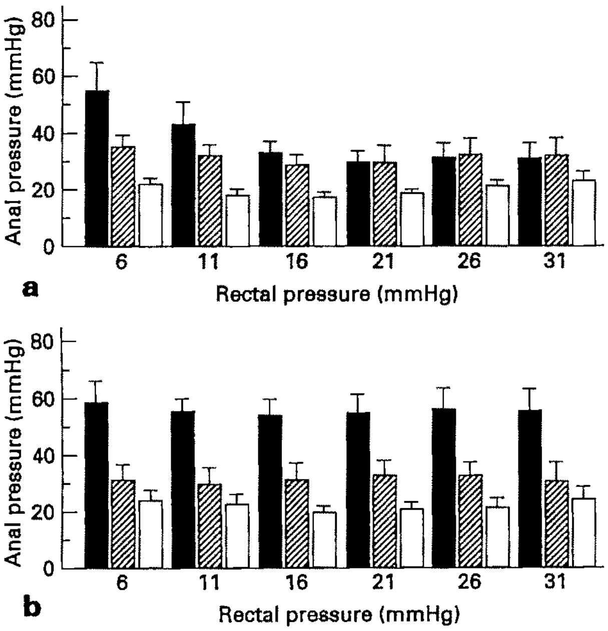

Fig. 1 Pressures recorded in **a** upper and **b** lower parts of the anal canal as a function of rectal pressure during phasic isobaric distension of the rectum in patients with rectal prolapse (☐) or faecal incontinence without rectal prolapse (▨) and in healthy controls (■). Pressures differed significantly between groups in both upper and lower parts ($P = 0{\cdot}023$ and $P < 0{\cdot}001$ respectively). (Two-way analysis of variance with repeated measures)

Rectal adaptation and perception

Pressure steps of distension significantly modified rectal adaptation for all recorded volumes and rectal perception ($P < 0{\cdot}001$ for all parameters, two-way repeated-measures analysis of variance). Both volumes and perception scores were increased with increased rectal distension. *Fig. 2* shows rectal adaptation to isobaric distension according to the pressure step of distension and the study group. A

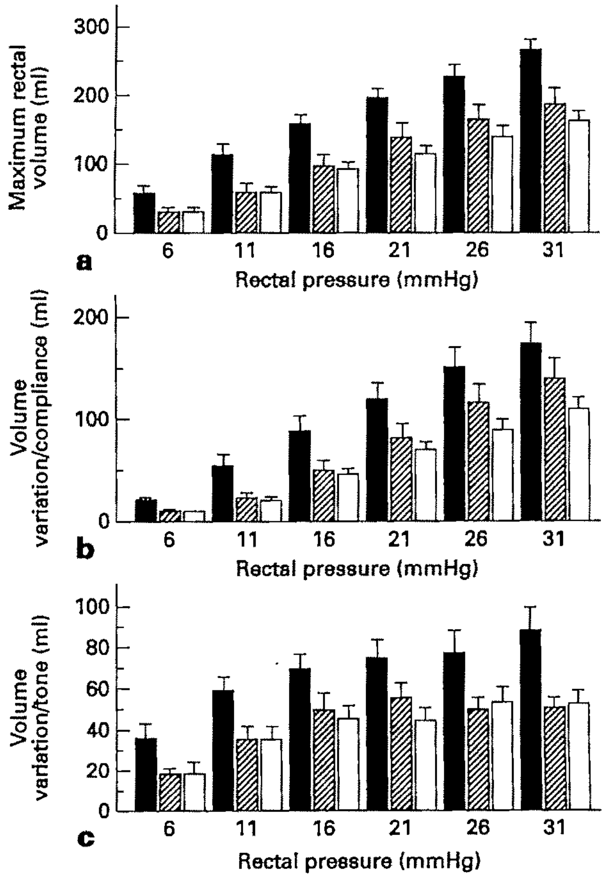

Fig. 2 Rectal volume as a function of rectal pressure during phasic isobaric distension of the rectum in patients with rectal prolapse (☐) or faecal incontinence without rectal prolapse (▨) and in healthy controls (■). **a** Rectal volume recorded at the end of each pressure plateau (maximum rectal volume). $P = 0{\cdot}007$. **b** Rectal volume recorded at the end of ascending pressure variation (volume variation related to compliance). $P = 0{\cdot}037$. **c** Variation in rectal volume recorded during each pressure plateau (volume variation related to tone). $P = 0{\cdot}003$. (Two-way analysis of variance with repeated measures)

group effect was observed for all types of recorded rectal volumes. Differences between groups did not depend on the pressure of distension, except when maximum rectal volumes were analysed (pressure × group interaction; $P = 0.005$). Compared with healthy subjects, maximum volumes (mean −41 per cent) and rectal volumes related to compliance (mean −43 per cent) and to tone (mean −38 per cent) were significantly decreased in the rectal prolapse group ($P = 0.005$, $P = 0.004$ and $P = 0.003$ respectively). For volumes related to rectal tone, differences between these two groups did not depend on the pressure step of distension (no pressure × group interaction). In contrast, prolapse and incontinence groups did not differ with respect to rectal adaptation, irrespective of the parameter (−12, −18 and −3 per cent respectively) and the step of distension considered.

Perception scores to distension did not differ significantly between patients with a rectal prolapse and healthy subjects ($P = 0.52$). However, scores for both groups differed from those in patients in the incontinence group who experienced blunted sensation ($P = 0.025$). Compared with those with rectal prolapse, blunted sensation in the incontinence group depended on the pressure of distension (pressure × group interaction; $P = 0.049$): differences were more pronounced between 16 and 26 mmHg.

Discussion

Controversy concerning incontinence in rectal prolapse suggests that at least three abnormal processes of motility may be involved, at anal, rectal or sigmoid levels.

In this study, anal pressures were particularly low in the rectal prolapse group both in the resting state and during distension. This is in accordance with previous manometric studies with basal or ambulatory recordings[10–13,22,23]. Interestingly, mean resting and squeeze pressures as well as internal anal sphincter responses to distension significantly differed between prolapse and incontinence groups despite similar mean incontinence scores. These differences may be explained by internal sphincter damage, pudendal neuropathy, prolonged internal anal sphincter inhibition or a combination of these pathogenic factors. Sphincter damage was not an explanatory factor in the present study as there was no difference between study groups in the incidence of sphincter defects. Nevertheless, such low squeeze increments are rather unusual in rectal prolapse; they may partly contribute to the incontinence recorded in the present study. Thus substantial nerve damage may occur in patients with rectal prolapse as suggested by a more pronounced perineal descent in this study and by more prolonged pudendal nerve latencies shown in a recent retrospective analysis[30]. Finally, frequent transient or prolonged internal anal sphincter relaxations may also explain these differences, as already suggested by ambulant manometric recordings: rectoanal inhibitory reflexes are sometimes difficult to elicit in up to 72 per cent of cases[13] and electromyographic activity of the internal anal sphincter is markedly reduced[14]. Rectal prolapse itself may induce high rectal pressure waves and simultaneous internal anal sphincter inhibition which is partially reversed after surgery[14]. In contrast, the present study did not provide evidence for increased rectal activity or transient internal anal sphincter inhibition as assessed by manometric recordings (motor indices, maximum rectal pressures), although the experimental protocol and equipment necessitated reduction of prolapse. However, poor recovery of anal parameters after surgical treatment of prolapse does not support the dubious role of anal pressures in continence[9–11,13,22,23].

Proctometrography using rapid volumic distension is the reference method for analysis of rectal adaptation. Its reproducibility is usually high with low volumes of distension but is lacking with increasing volumes[31,32]. The electronic barostat is a very sensitive method for modulating rectal stimulation and recording rectal adaptation[27]. Isobaric distensions were chosen because intraindividual reproducibility was suboptimal in healthy volunteers and variation did not reach 10 per cent during phasic distension (data not shown). Moreover, this technique allowed measurement of two parameters of rectal adaptation to distension (compliance and tone). Rectal adaptation to distension has mainly been investigated before and after surgery for rectal prolapse[3,8,33–36]. Control groups are lacking in several studies and data with important variability related to isovolumic distension from a manometric device require cautious interpretation[37,38]. Using isobaric distension, this study showed impaired rectal adaptation in both groups of patients compared with healthy subjects. A poor adaptation to rectal filling may reflect a negative feedback of anal weakness without functional significance because adaptation did not differ between prolapse and incontinence groups. Nevertheless, impaired rectal adaptation may also induce faecal leakage by itself. Surgical and experimental data support this latter hypothesis. Rectal adaptation has been reported to be markedly improved by rectopexy[3,10,19,36] and improvement of continence correlated with rectal volumes[3]. In contrast, several surgical procedures, such as Wells rectopexy, lateral ligament division and Delorme's procedure, produce stability or a decrease in rectal capacity[8,33–36]. Delorme's procedure reduced rectal compliance to one-tenth of the preoperative value in one manometric study; 69 per cent of patients suffering from faecal leakage remained incontinent after operation[35]. Wells rectopexy reduced rectal capacity to one-half of preoperative values in one study using isobaric distension; incontinence was not markedly affected by this reduced parameter but 75 per cent of patients experienced normal continence before operation[8]. Finally, using an isobaric distension model, rectal adaptation was scarcely decreased in patients with incontinence and no anal weakness compared with that in those with anal weakness[39].

High rectal pressure waves have been recorded in patients with internal or overt rectal prolapse during ambulatory monitoring[13,14] or serial distension of the rectum[24]. Thus, the hyper-reactive rectum induces reversed rectoanal pressure gradients which are likely to lead to both faecal leakage and worsening of the prolapse[24]. Once again, these features are improved by surgery for rectal prolapse[14]. The present study was not able to demonstrate such abnormal motility but differences in methodology may explain these discrepancies, in that lasting isobaric distensions and software sampling frequencies block rapid pressure variations. An increase in sigmoid motility has also been demonstrated in incontinent subjects with prolapse while continent patients show normal patterns[40]. Thus, postoperative improvement of continence may be related to a reversed pressure gradient induced by the surgical procedure at the sigmoid level[28].

In conclusion, patients suffering from faecal incontinence and rectal prolapse experienced profound impairment of motility at different anatomical levels. Whether these abnormalities are at the source of faecal leakage or represent an epiphenomenon remains questionable but a body of evidence suggests that motility and adaptation of the rectum may be the main culprits. Pathogenic mechanisms may involve anatomic neuropathy rather than wall fibrosis because impaired rectal adaptation to isobaric distension is similar in prolapse and incontinence groups. These findings may have implications for the choice of rectal prolapse surgery, especially when lateral ligament division, extensive dissection or a Delorme procedure is planned.

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Tube caecostomy to protect rectal anastomoses

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Background Low rectal anastomoses are associated with a substantial risk of anastomotic leakage. Tube caecostomy offers a potentially simple method of anastomotic protection.

Methods Some 226 patients undergoing restorative rectal resection with on-table colonic lavage and tube caecostomy over an 11-year period were reviewed. Endpoints selected included clinical anastomotic leakage, requirement for a subsequent formal stoma and complications of tube caecostomy.

Results Overall, clinical anastomotic leakage occurred in 25 patients with a caecostomy (11·1 per cent). All leaks were noted among patients in whom caecostomy protection had been used after low anterior resection, giving a leak rate of 14·9 per cent (25 of 168) for this group of whom 17 (10·1 per cent) required reoperation and a formal stoma, and five (3·0 per cent) died. Complications of caecostomy or prolonged drainage after tube removal occurred in ten (4·4 per cent) and 15 (6·6 per cent) patients respectively. There were two cases of life-threatening invasive infection.

Conclusion Tube caecostomy provides inadequate protection of rectal anastomoses; complications are common and may be life threatening.

Colorectal or coloanal anastomosis deep in the pelvis is associated with a high risk of anastomotic leakage[1–3]. There is no uniformity of approach regarding use of a proximal stoma to protect low anastomoses[2]. Having used on-table antegrade colonic lavage for all left colonic and rectal resections since 1980, the authors decided on a compromise approach, namely a large-calibre caecostomy[5]. Like Rosin[6], they argued that with a completely empty colon the caecostomy would vent sufficient gas and fluid to defunction the anastomosis while it healed.

The experience of a single surgical team, using a policy of tube caecostomy to 'protect' rectal anastomoses, is presented in terms of efficacy and safety.

Patients and methods

Patients undergoing restorative resection of the rectum or rectosigmoid colon between January 1983 and April 1994 were identified from prospective records using the clinical case notes; a standard pro forma was completed detailing the operative procedure, use of caecostomy, its size and clinical outcome.

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Indications for tube caecostomy included low anterior resection with total mesorectal excision (TME), higher resections if there was any concern about the integrity of the anastomosis and emergency operations for perforation or obstruction of the rectum or sigmoid colon.

Large de Pezzer catheters (32–36 Fr), with ends trimmed for easier removal, were placed into the caecum where they were held with purse-string sutures and further secured by sutures between the caecum and parietal peritoneum at the point of exit. The tubes were irrigated with 0·9 per cent saline 50 ml twice daily. They were retained for 2 weeks or longer when there was anastomotic leakage.

Results

A total of 395 patients underwent restorative rectal or rectosigmoid resection during the study period (*Table 1*). Thirty-four operations (8·6 per cent) followed an acute presentation; 360 (91·1 per cent) were for carcinoma.

Table 1 Defunctioning techniques and outcome after rectal or rectosigmoid resection

	No.	Clinical leak	Stoma for leak	Fatal leak
Low anterior and total mesorectal excision				
Caecostomy	168 (12)*	25 (14·9)	17 (10·1)	5 (3·0)
Loop stoma	33 (5)*	5	0	0
No defunction	38 (0)*	3	2	0
Total	239	33 (13·8)	19 (7·9)	5 (2·1)
Rectosigmoid resection				
Caecostomy	58	0	0	0
Loop stoma	8	0	0	0
No defunction	90	3	3	0
Total	156	3 (1·9)	3 (1·9)	0 (0)
Overall total	395	36 (9·1)	22 (5·6)	5 (1·3)

Values in parentheses are percentages except *number of transanal anastomoses

Tube caecostomies were used in 226 patients, loop stomas in 41 patients and no defunction in 128 patients. Clinical anastomotic leakage with tube caecostomy occurred in 25 patients (11·1 per cent). All leaks were among patients undergoing low anterior resection with TME (*Table 1*). In this group the leak rate was 14·9 per cent. Seventeen patients (10·1 per cent) required reoperation and a definitive stoma, and the leak was fatal in five patients (3·0 per cent).

In the presence of a tube caecostomy anastomotic leakage often presented insidiously, possibly because of the partial defunction/drainage provided by the tube. The mean time between resection and reoperation was 20 (range 11–42) days.

The overall leak rate in patients undergoing rectosigmoid resection was low at three of 156 (1·9 per cent). Sixty-five of these patients had undergone caecostomy without leakage.

Most tube caecostomies were trouble free; even occasional inadvertent removal of the tube caused no problems. However, ten patients (4·4 per cent) had caecostomy-related complications and 15 (6·6 per cent) had prolonged drainage after removing the tube. Four patients developed pericatheter cellulitis, two developed a caecostomy-site hernia (repaired) and two required operative closure of what had become a chronic faecal fistula.

Two further patients suffered major caecostomy-related sepsis. In the first, pericaecostomy necrotizing fasciitis required wide debridement, formal caecostomy and weeks of intensive care. The second developed excavating abscesses between the external and internal oblique muscles and required a major operative drainage procedure. Both patients recovered.

Discussion

The major findings from this study are that tube caecostomy is an inadequate means of 'protecting' a rectal anastomosis, and that it may occasionally cause life-threatening invasive sepsis.

Benacci and Wolff[7] have recently reported the Mayo Clinic experience with tube caecostomy. Among 67 patients, the procedure was used to protect a distal anastomosis in only eight. Clark and Hubay[8] reported 161 tube caecostomies of which 97 were performed to decompress a distal anastomosis. Clinical anastomotic leakage occurred in 2 per cent. However, only 13 patients had had an anterior resection; the remainder were more proximal. Stainback *et al.*[9] reported routine use of tube caecostomy in 235 patients undergoing elective left hemicolectomy or rectosigmoid resection with a mortality rate of 3·4 per cent (no death due to anastomotic leakage). However, the number of anterior or low anterior resections was not specified. Each of these reports generally favoured tube caecostomy, although its specific value in protecting low rectal anastomoses was not addressed.

Clinical evidence of anastomotic leakage has been reported in up to 15 per cent of patients undergoing elective low anterior resection with TME without any means of defunction[2]. Reoperation and formation of a stoma has been required in 3–8 per cent of such patients[2,10,11]. These results, obtained without attempting to defunction, are similar to the present leak and reoperation rates (14·9 and 10·1 per cent) in 168 patients with a 'protective' caecostomy, suggesting that caecostomy confers no benefit. The most likely explanation for the poor results with caecostomy is that the procedure does not in fact decompress or defunction the distal colon or rectum. Prophylactic use of a defunctioning loop stoma at the time of low anterior resection appears to reduce the severity of illness caused by leakage (even if leaks are not prevented) and has been associated with a reoperation rate for leakage of 0·8 per cent, considerably lower than that seen using a tube caecostomy in the present study[2]. Moreover, leaks distal to a loop stoma are likely to heal, often permitting delayed closure of the stoma with an acceptable functional result. However, leakage without a stoma or with a caecostomy only leads to a more severe clinical illness often requiring that the anastomosis be taken down with formation of an end stoma. Restoration of intestinal continuity and stoma closure are less likely thereafter[10].

Previous reports have described a range of complications from tube caecostomies[7,12]; complications or prolonged drainage (after tube removal) were encountered in 11·1 per cent of the present patients and 2·7 per cent required reoperation.

This experience suggests that tube caecostomy should no longer be used to 'protect' rectal anastomoses. The authors have switched to using a temporary loop ileostomy to defunction low rectal anastomoses since 1994.

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Effects of early postoperative 5-fluorouracil and ageing on the healing capacity of experimental intestinal anastomoses

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Background Results from a previous study suggested that advanced age does not affect early repair of experimental intestinal anastomoses. The present study aimed to establish whether anastomotic healing is impaired more easily in old animals by immediate postoperative chemotherapy.

Methods Young adult (2–3 months) and old (27–30 months) rats underwent resection and anastomosis of both ileum and colon. Within each age group, subgroups received intraperitoneal saline or 5-fluorouracil in a dose of 15 or 20 mg per kg per day from the day of operation onwards. After 7 days, anastomotic healing was assessed by wound strength and collagen deposition in the wound area.

Results No differences were found between young and old control groups. The higher dose of fluorouracil induced severe loss of strength with concomitant reduction of wound collagen, which was similar in both age groups (ileum: from 52(13) to 24(8) volume per cent in young animals and from 56(10) to 20(9) volume per cent in old animals; colon: from 58(10) to 37(18) volume per cent in young animals and from 65(5) to 30(17) volume per cent in old animals). The lower dose of fluorouracil induced a significantly greater loss of strength, measured as the bursting pressure, in the old animals (150(49) *versus* 201(59) mmHg in colon of young rats).

Conclusion In this model early anastomotic repair in older animals proceeds normally under optimal conditions, but it is more easily disturbed in the presence of fluorouracil.

It is often stated, and widely believed, that the capacity for wound repair declines with advancing age[1]. However, a recent critical review of cutaneous healing points out that this dogma remains largely unsubstantiated[2]. Most surgeons believe that advanced age is a factor which predisposes to anastomotic dehiscence[3]. Since anastomotic failure is a most serious complication, attended by high morbidity and mortality rates, it is important to know to what extent putative negative factors may impair intestinal healing and therefore should weigh heavily in an eventual decision to forgo construction of a primary anastomosis after intestinal resection. Retrospective patient studies do not unequivocally support the conclusion that age is an independent factor[4–6]. A recent multivariate analysis of factors contributing to anastomotic leakage did not confirm age to be a predictive variable[7].

The healing process can be affected by a multitude of factors[8] and most patient studies have not been adequately controlled for concurrent pathology. Therefore, it can be argued that the potential of individual factors to impair anastomotic healing can best be assessed in animal models. The authors have recently reported that anastomotic repair is essentially similar in healthy young and old rats, indicating that advanced age is not a negative factor[9]. However, it could very well be that the repair process in old animals is more easily disturbed by the presence of adverse conditions, such as concurrent chemotherapy. Since patients with cancer constitute an important part of the older patient population presenting for gastrointestinal surgery and there exists growing interest in immediate postoperative regional adjuvant chemotherapy based on 5-fluorouracil[10,11], this combination was examined.

Materials and methods

Animals

Two groups ($n = 45$ each) of male rats of the outbred strain Cpb:WisWinkelman (Winkelman, Borchen, Germany), aged 2–3 months and 27–30 months, were used. The old animals were provided by Dr F. J. van der Staak, Tropon Werke, Cologne, Germany. The rats were housed under standardized conditions and received pelleted food (diet RMH-B; Hope Farms, Woerden, The Netherlands) and tap water *ad libitum*. The animals were kept for at least 1 week before operation to acclimatize. Only rats that looked healthy and had no palpable tumours were used in the experiment.

In each age group, 15 animals acted as controls and 30 were treated with 5-fluorouracil, 15 with a high dose (see below) and 15 with a lower dose. In all six groups of 15 rats, ten were used for measurement of anastomotic strength and five for morphometric analysis of collagen in the wound area.

The study was approved by the Animal Ethics Review Committee of the Faculty of Medicine, University of Nijmegen.

Operative procedure

All rats were anaesthetized with isoflurane (4 volume per cent) administered by mask. After induction, anaesthesia was maintained with isoflurane 1·5 volume per cent and a single dose of morphine hydrochloride (1 mg per kg body-weight) was administered subcutaneously.

Surgery was performed under semisterile conditions, using an operating microscope. The abdomen was opened through a median incision of approximately 4 cm. A 1-cm length of colon was resected 3 cm proximal to the peritoneal reflection and an end-to-end anastomosis was constructed using eight single-layer inverting interrupted 8/0 Ethilon sutures (Ethicon, Norderstedt, Germany). Subsequently, resection and anastomosis was repeated in the ileum, 15 cm proximal to the caecum. The abdominal fascia was closed with silk, and the skin with staples placed 1 cm apart.

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Administration of 5-fluorouracil

Fluorouracil was given intraperitoneally at a dose of 15 or 20 mg per kg body-weight. In previous experiments it was established that a daily dose of 20 mg per kg body-weight represents the highest dose which, in combination with operation, does not result in a significant mortality rate[12]. The drug was administered once a day, immediately after operation and for the next 6 days, at a concentration of 1 mg/ml in saline. Control groups received saline only.

Analytical procedures

All rats were killed 7 days after operation by cardiac puncture and bleeding. After opening the abdominal wound and identifying the anastomoses, the adhesions were cut as far as possible without injuring the intestine.

To assay anastomotic strength an intestinal segment with the anastomosis in the middle was removed, with the sutures left in place and analysed sequentially for bursting pressure and breaking strength[13].

To perform morphometric analysis of collagen, a 3-cm segment of the intestine, including the anastomosis, was collected. Tissue processing and analysis have been described elsewhere[14]. This procedure allows calculation of the volume fraction of collagen in the wound area.

Statistical analysis

Differences between groups were tested for significance with a rank sum two-sample test (Mann–Whitney *U* test), with significance levels set at 5 per cent. If multiple comparisons were made, pairwise comparisons of groups were performed using a level of significance of $\alpha' = 2\alpha/k$, where k is the number of pairwise comparisons.

Results

Three of 90 animals died prematurely. In the groups receiving 5-fluorouracil 15 mg/kg one young rat died 6 days after operation. In the groups receiving 5-fluorouracil 20 mg/kg two old rats died, one within 24 h (probably from respiratory problems) and one after 3 days. Examination of these animals revealed no signs of anastomotic insufficency.

After operation, all rats lost weight (*Fig. 1*). The mean(s.d.) peroperative weight was 313(29) g for the young rats ($n = 30$) and 475(42) g for the old rats ($n = 30$). In the control groups, the absolute weight loss on day 1 was similar in both young and old animals, while the mean relative weight loss constituted 8 and 4 per cent respectively of the weight at operation. On day 7, the young rats had regained their preoperative weight, while the mean weight loss in the old rats was 6 per cent ($P < 0\cdot01$ *versus* young rats). Administration of 5-fluorouracil led to progressive weight loss, increasingly so at the highest dose. Young animals receiving the low dose of 5-fluorouracil had lost 17 per cent of their peroperative body weight at day 7 ($P < 0\cdot01$ *versus* controls) and those receiving the high dose lost 28 per cent ($P < 0\cdot01$ *versus* low-dose group). In the old rats these values were 14 per cent in the low-dose group ($P < 0\cdot01$ *versus* controls) and 19 per cent in the high-dose group ($P = 0\cdot02$ *versus* low-dose group).

Individual values for the anastomotic bursting pressure, a measure of the ability of the healing intestine to withstand intraluminal pressure, are shown in *Fig. 2*. Some 7 days after operation, in the control groups the anastomosis had grown stronger than the adjacent tissue causing rupture to occur outside the wound area. Here, the values shown can be taken to represent the minimum bursting pressure of the anastomosis proper. In the ileum, mean values in young and old rats were similar, while in the colon the mean bursting pressure was significantly higher in the old rats (mean(s.d.) 210(24) *versus* 186(30) mmHg; $P = 0\cdot03$). The maximum tolerated dose of 5-fluorouracil (20 mg per kg per day) strongly and significantly ($P < 0\cdot01$) suppressed the development of anastomotic strength. In all cases except one, rupture occurred within

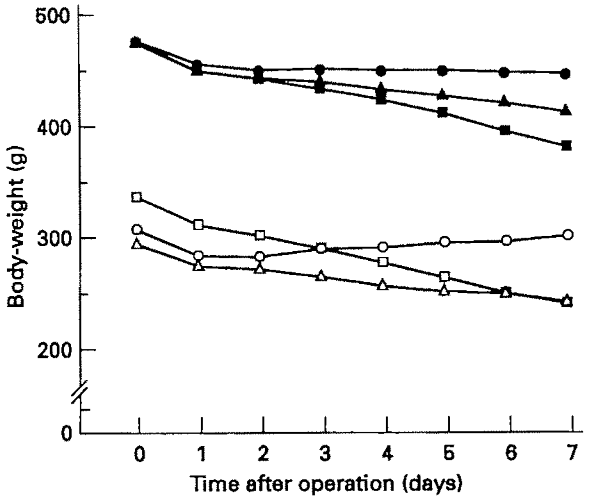

Fig. 1 Change in body-weight after operation. Mean values are shown for groups ($n = 10$) of young (open symbols) and old (closed symbols) rats. ○/●, Control groups; ▲/△, groups receiving 5-fluorouracil 15 mg per kg per day; □/■, groups receiving 5-fluorouracil 20 mg per kg per day

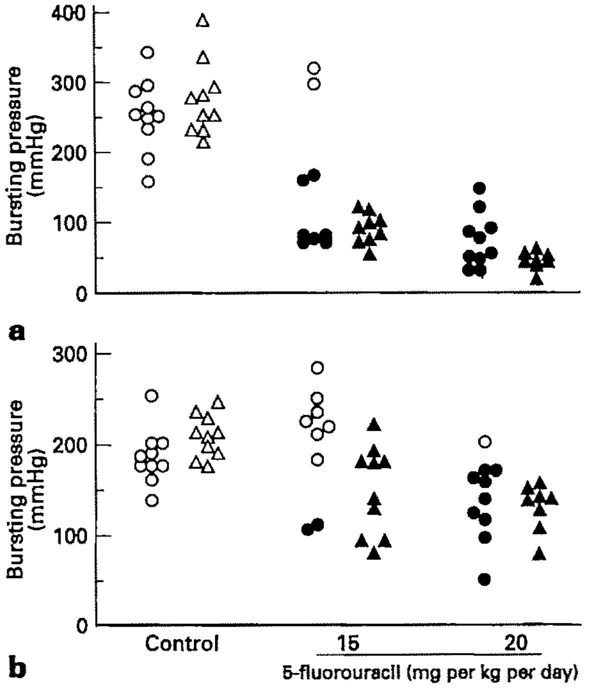

Fig. 2 Anastomotic bursting pressure in ileum (a) and colon (b) from individual animals. Closed symbols indicate rupture within the suture line and open symbols rupture outside the suture line. ○/●, Young rats; ▲/△, old rats

the suture line. Mean values were similar in young and old rats: in the ileum 71(37) *versus* 44(12) mmHg and in the colon 137(44) *versus* 130(26) mmHg respectively. However, the two age groups reacted differently to the lower dose of 5-fluorouracil (15 mg per kg per day), particularly so with respect to the colonic bursting pressure. In the young animals only two of nine ruptures occurred within the suture line and in the old animals ten of ten ($P < 0{\cdot}01$, Fisher's exact test). In addition, the mean anastomotic bursting pressure was significantly lower in the old rats (150(49) *versus* 201(59) mmHg, $P = 0{\cdot}03$). In the ileum, the difference was less obvious, although the mean bursting pressure was again lower in the old animals (90(21) *versus* 146(97) mmHg).

The anastomotic breaking strength in all groups that had received 5-fluorouracil was significantly lower than that in the respective control groups, with the exception of the colonic strength in old rats receiving the high dose (*Fig. 3*). No significant differences were found between young and old animals.

Treatment with low-dose fluorouracil did not result in diminished accumulation of anastomotic collagen (*Fig. 4*). However, administration of the high dose significantly impaired collagen fibril formation within the anastomosis. In the ileum, mean(s.d.) values decreased from 52(13) to 24(8) volume per cent ($P = 0{\cdot}016$) in the young animals and from 56(10) to 20(9) volume per cent ($P = 0{\cdot}01$) in the old animals. In the colon similar reductions were found: from 58(10) to 37(18) volume per cent ($P = 0{\cdot}05$) in the young rats and from 65(5) to 30(17) volume per cent ($P = 0{\cdot}01$) in the old rats. No differences were found between young and old animals.

Discussion

Anastomotic healing proceeds equally well in young adult and old animals, if no factors are present which negatively affect mechanisms from the repair sequence. Under adverse conditions, as is the case during perioperative treatment with 5-fluorouracil, healing appears to be more severely disturbed at advanced age. It appears that sufficient capacity is left in old animals to allow healing under optimal conditions, but that the reserve capacity – necessary under adverse conditions – has diminished.

Clinical data on the effect of advanced age on the frequency of anastomotic dehiscence in the large bowel are contradictory[4–7]. Experimental data unequivocally support the clinical studies that have found age not to be an independent factor for anastomotic failure. Repair has been reported to proceed at a similar rate in young and old rats, both in linear incisions in the duodenum[15] and in ileal and colonic anastomoses[9,16]. In addition, a recent review points out that the common wisdom that ageing impairs (cutaneous) healing appears to be based largely on experimental and clinical studies which have not been designed adequately[2]. We believe that old age alone is not a factor that lowers anastomotic strength. This does not

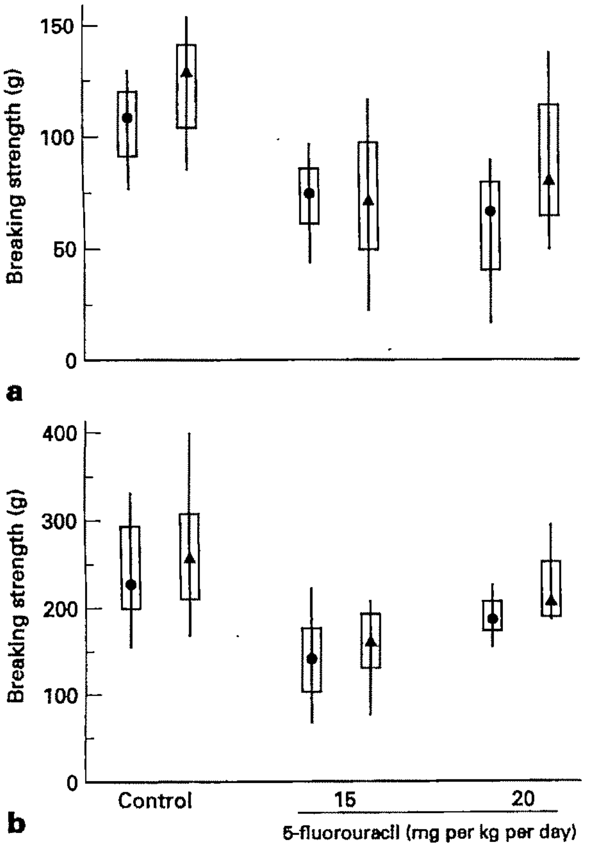

Fig. 3 Anastomotic breaking strength in ileum (a) and colon (b) from young (●) and old (▲) rats. Symbols represent medians, bars indicate range and boxes the 95 per cent confidence interval. $n = 10$ for each group, except the young low-dose fluorouracil group ($n = 9$) and the old high-dose fluorouracil group ($n = 8$)

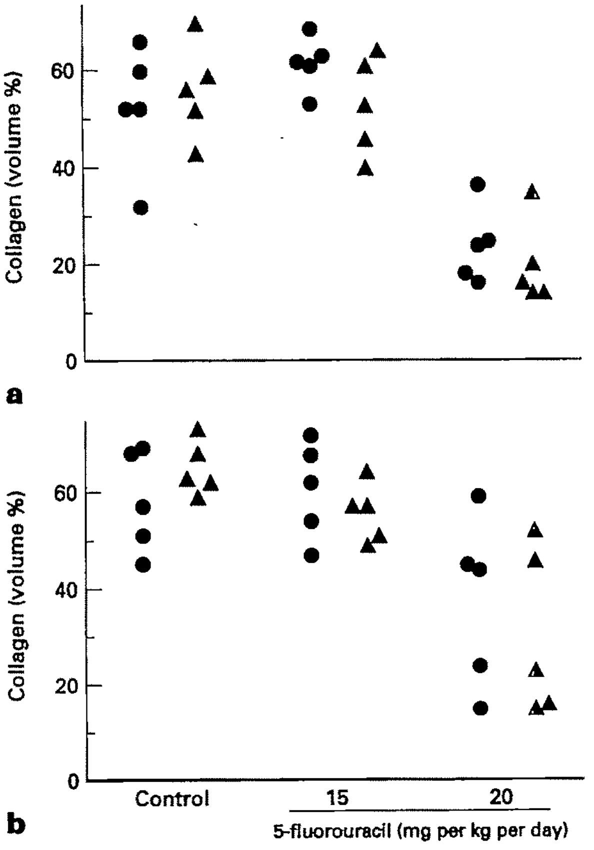

Fig. 4 Morphometric analysis of the collagen concentration within the anastomosis in ileum (a) and colon (b) from individual young (●) and old (▲) rats

preclude the possibility that intestinal anastomoses in the elderly heal poorly in the presence of other negative factors.

In the current experiments a negative factor was introduced by the immediate postoperative administration of the antineoplastic drug 5-fluorouracil. Previous studies by others[17] and in the authors' laboratory[12,13,18] have delineated the negative effects of 5-fluorouracil on anastomotic healing in young adult animals.

In the present study the higher dose of 5-fluorouracil used, 20 mg per kg per day, impaired anastomotic strength to the same extent in young and old animals. This dose of 5-fluorouracil was shown previously to lower anastomotic collagen synthetic capacity[13], possibly by reducing the number of fibroblasts and directly inhibiting fibroblast collagen synthesis[19]. Apparently, this treatment burdened the healing capacity in young animals to such an extent that maximal suppression of repair occurred. As a consequence, the end result was the same as in old rats.

Administration of the lower dose of 5-fluorouracil, 15 mg per kg per day, still significantly lowered anastomotic bursting pressure and breaking strength. However, a significant difference became apparent between the two age groups with regard to the bursting pressure, especially in the colon. While bursting invariably occurred within the suture line in the old animals, this was not the case in the young rats, in which the wound had mostly grown stronger than the surrounding tissue. Interestingly, this difference did not appear in the breaking strength. Both parameters reflect wound strength, but the breaking strength is a measure of the capacity to withstand longitudinal forces while the bursting pressure represents the ability to resist intraluminal pressure and therefore is perhaps physiologically more meaningful. Also, the bursting pressure will be affected by a very small rupture of the intestinal wall, while the breaking strength will remain intact after such a localized process.

Deposition of collagen in the wound was the same in both age groups and similar to that in untreated controls. It thus seems unlikely that the increased loss of strength in the old rats, observed after treatment with the lower dose of 5-fluorouracil, was caused by a reduction in collagen synthesis. It may be that the organization of the anastomotic collagen is different[20] in older animals, rendering it more susceptible to local degradation by matrix metalloproteinases. Collagenase expression is increased and its regulation by cytokines is altered in fibroblasts from old donors and cells which have aged *in vitro*[21,22]. Such a mechanism does not necessarily lead to obvious differences in strength between the age groups at the higher 5-fluorouracil dose, since here the massive negative effect on collagen accumulation in the wound area alone maximally suppresses wound strength. An eventual increase in local degradation of collagen would show no additional effect.

Under these experimental conditions, immediate postoperative 5-fluorouracil reduced anastomotic strength more strongly in the older age group. In the clinical situation, when antineoplastic drugs are used, advanced age should perhaps be considered as a factor which increases the chance of anastomotic failure.

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Emergency resection and primary anastomosis for left-sided obstructing colorectal carcinoma in the elderly

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Background Emergency colorectal surgery in the elderly has been associated with a high mortality rate. Although the current trend for the management of obstructing left-sided colorectal carcinoma favours primary resection and anastomosis, the safety and benefits of this approach in the elderly have not been studied.

Methods Some 57 elderly (aged more than 70 years) and 59 younger patients underwent emergency resection of an acutely obstructing left-sided colorectal carcinoma. Postoperative results in the two groups were compared.

Results The primary resection rate was 95 per cent in the elderly and 89 per cent in younger patients ($P = 0{\cdot}70$), with a primary anastomosis rate of 84 per cent and 78 per cent respectively ($P = 0{\cdot}64$). Elderly patients had a significantly higher incidence of premorbid risk factors and postoperative cardiorespiratory complications but no increase in surgical complications. Anastomotic leaks occurred in 6 per cent of the elderly and 4 per cent of younger patients ($P = 0{\cdot}65$), and the hospital mortality rate was 9 and 5 per cent respectively ($P = 0{\cdot}48$).

Conclusion Emergency resection and primary anastomosis for left-sided obstructing colorectal carcinoma can be performed with favourable outcome in the elderly and should be the treatment of choice in most elderly patients.

Colorectal carcinoma is a common malignancy in developed countries. With an ageing population, there is an increasing number of elderly patients with colorectal carcinoma[1,2] who are more likely to present as an emergency than younger patients[3,4]. Recent studies have demonstrated the safety of elective resection of colorectal carcinoma in the elderly, but the operative mortality rate has remained significantly higher in elderly than younger patients undergoing emergency colorectal surgery[3–7].

Intestinal obstruction is the commonest emergency presentation of colorectal carcinoma. For obstructing tumours proximal to the splenic flexure, right or extended right hemicolectomy with ileocolic anastomosis is the accepted practice. The management of left-sided obstructing tumours is more controversial. Current trend favours primary resection and anastomosis[8–10] but Hartmann's procedure remains a popular choice among general surgeons[11], and a minority of surgeons are still proponents of the three-stage approach[12,13]. In particular, the safety of primary resection and anastomosis in the elderly remains questionable as this was usually performed in selected low-risk patients in reported series[10]. With the growing elderly population, it is important to establish the safety and benefits of this approach in the elderly. This study evaluated the results of emergency resection and primary anastomosis for obstructing left-sided colorectal carcinoma in the elderly.

Patients and methods

Between March 1989 and September 1997, 126 consecutive patients underwent emergency operation within 24 h of admission for acute obstruction resulting from left-sided colorectal carcinoma distal to the splenic flexure, including rectal tumours. A further 48 patients admitted with subacute obstruction due to left-sided colorectal carcinoma during the same period underwent semiurgent operation after 24 h and were excluded from the study.

All patients were admitted directly through the accident and emergency department, under the care of a team of specialist colorectal surgeons. Premorbid conditions such as cardiorespiratory disease, renal insufficiency, cirrhosis and diabetes mellitus were documented, and physicians were consulted if necessary for optimal perioperative management. Preoperative resuscitation included aggressive fluid replacement with monitoring of central venous pressure and urine output, correction of electrolyte imbalance and nasogastric decompression. Flexible sigmoidoscopy or colonoscopy was performed whenever possible to confirm the site and nature of obstruction. Intravenous prophylactic antibiotics (cefuroxime and metronidazole) were given.

Since 1989 all those with left-sided obstructing colorectal carcinoma underwent primary resection and anastomosis if the condition of the patient and the bowel allowed. The method of intraoperative colonic lavage for primary anastomosis has been described previously[14]. After operation patients were monitored carefully and those with severe premorbid risk factors or requiring inotropic or ventilatory support were admitted to the intensive care unit (ICU).

Data on all patients were collected prospectively in a computerized database. Sixty-six patients (52 per cent) were aged 70 years or less and 60 (48 per cent) were older than 70 years, which was defined as elderly; the perioperative results of these two groups were compared. Hospital mortality included all deaths in hospital during the emergency admission. Hospital deaths were excluded in the analysis of hospital stay.

Statistical analysis

Statistical analysis was performed with the Mann–Whitney *U* test for ordinal variables and the χ^2 test with Yates' correction (or Fisher's exact test where appropriate) for nominal variables. $P < 0{\cdot}05$ was considered significant.

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Results

Types of surgery

The sites and stages of the tumours were similar between the two groups (*Table 1*). The types of emergency surgery performed are shown in *Table 2*. Primary resection rates were similar in the elderly (95 per cent) and younger patients (89 per cent) (*P* = 0·70). Resection was curative in 47 elderly (82 per cent) and 46 younger patients (78 per cent) (*P* = 0·72). Primary anastomosis rates were 84 per cent (48 of 57) and 78 per cent (46 of 59) respectively (*P* = 0·64). Except for the use of stapling in four patients who had low anterior resection, primary anastomosis was performed with hand-sewn, one-layer, interrupted or standard two-layer sutures. No proximal protective stoma was used except in two patients with a positive air leak test after low anterior resection. Eleven elderly patients underwent subtotal colectomy with ileocolic anastomosis, eight for impending caecal rupture due to tear or gangrene and three as the elected procedure. In contrast, ten younger patients underwent subtotal colectomy as the procedure of choice and only three underwent subtotal colectomy for caecal gangrene. Significantly more elderly patients required subtotal colectomy for gangrenous caecum than younger patients (*P* = 0·04).

Table 1 Patient demographics

	≤70 years (*n* = 66)	>70 years (*n* = 60)	*P*†
Mean(s.d.) (range) age (years)	59·8(9·6) (29–69)	78·0(7·5) (71–91)	
Sex ratio (M:F)	42:24	36:24	0·68
Site of tumour*			0·39
Descending colon	9 (14)	11 (18)	
Sigmoid colon	36 (55)	37 (62)	
Rectosigmoid junction	10 (15)	4 (7)	
Rectum	11 (17)	8 (13)	
Dukes classification*			0·77
A	2 (3)	1 (2)	
B	28 (42)	28 (47)	
C	22 (33)	22 (37)	
'D'	14 (21)	9 (15)	

*Values in parentheses are percentages. † χ^2 test

Table 2 Types of emergency surgery

Surgical treatment	≤70 years (*n* = 66)	>70 years (*n* = 60)
Primary resection		
With primary anastomosis		
Left hemicolectomy	5	10
Sigmoid colectomy	19	18
Anterior resection	7	7
Low anterior resection	2	2
Subtotal colectomy	13	11
Without anastomosis		
Hartmann's operation	10	8
Colectomy with colostomy and mucous fistula	3	0
Subtotal colectomy with ileostomy	0	1
Total	59 (89)	57 (95)
No primary resection		
Temporary colostomy (three-stage procedure)	3	1
Permanent palliative colostomy	4	2
Total	7 (11)	3 (5)

Values in parentheses are percentages

The indications for resection without anastomosis were for palliation of locally advanced tumours (five younger and three elderly patients), intraoperative haemodynamic instability (three younger and three elderly patients), unfavourable bowel condition due to friable oedematous tissue or doubtful blood supply (five younger and two elderly patients) and the presence of a synchronous low rectal tumour in one elderly patient with an obstructing sigmoid tumour, who underwent Hartmann's procedure followed by subsequent excision of the rectal tumour. Four of the 13 younger patients but none of the elderly patients subsequently underwent reanastomosis.

Four patients had a temporary colostomy followed by elective resection because of poor haemodynamic status (one patient), severe bleeding tendency due to cirrhosis (one) or very low rectal tumour (two). Six patients had a permanent palliative colostomy in the presence of carcinomatosis peritonei or extensive metastatic disease.

Morbidity

Of patients who had primary resection, elderly patients had a higher incidence of premorbid cardiorespiratory risk factors and of postoperative cardiac and respiratory complications (*Table 3*). The incidence of surgical complications was similar in the two groups (*Table 3*). The clinical anastomotic leak rate was 4 per cent in younger patients and 6 per cent in the elderly (*P* = 0·65) (*Table 3*).

Mortality

The hospital mortality rate was 5 per cent in younger patients and 9 per cent in the elderly after primary resection (*P* = 0·48) (*Table 3*). Of the eight hospital deaths,

Table 3 Premorbid risk factors and postoperative outcome in patients undergoing primary resection

	≤70 years (*n* = 59)	>70 years (*n* = 57)	*P*
Premorbid risk factors			
Cardiac	5	19	0·002‡
Respiratory	0	5	0·02‡
Other	4	7	0·30‡
Medical complications*			
Cardiac	3	11	0·02‡
Respiratory	5	11	0·10‡
Other	1	3	0·50‡
Surgical complications			
Anastomotic leakage	2 of 46†	3 of 48†	0·65‡
Intra-abdominal abscess	2	1	0·56‡
Postoperative haemorrhage	0	1	0·50‡
Prolonged ileus (>7 days)	1	0	0·50‡
Wound infection	7	6	0·76‡
Hospital death	3	5	0·48‡
Postoperative ICU care	7	21	0·001‡
Median (range) hospital stay (days)	12·5 (7–56)	16·5 (7–74)	0·02§

*Cardiac complications included dysrhythmia, heart failure and myocardial infarction; respiratory complications included atelectasis, bronchopneumonia and aspiration pneumonia; other complications included stroke in one elderly patient and urinary tract infection in three other patients. †Number of patients with primary anastomosis. ICU, intensive care unit. ‡ χ^2 test or Fisher's exact test; § Mann–Whitney *U* test three occurred after segmental colectomy with primary anastomosis, three after subtotal colectomy and two after Hartmann's procedure. The cause of death was pneumonia in two younger and one elderly patients, myocardial infarction in two elderly patients, subphrenic abscess in one younger patient, intra-abdominal haemorrhage due to coagulopathy in a cirrhotic elderly patient and peritonitis due to anastomotic leakage in an 85-year-old patient who refused reoperation. Of the ten patients with colostomy alone, there was one hospital death in a younger patient due to malignant cachexia after a palliative colostomy.

Postoperative hospital stay

Postoperative hospital stay after primary resection was significantly longer in the elderly, and more elderly patients required ICU care (*Table 3*). Median hospital stay was longer after resection without anastomosis than after resection with primary anastomosis in both younger (19·0 *versus* 11·5 days, $P = 0{\cdot}02$) and elderly patients (20·5 *versus* 16·0 days, $P = 0{\cdot}4$).

Discussion

The traditional three-stage approach for left-sided obstructing colorectal carcinoma has become unpopular because of the high cumulative mortality and morbidity rates and long overall hospital stay[10]. However, Hartmann's procedure remains popular and has been recommended by some authors as the treatment of choice in the elderly[1,15]. The present authors' approach was primary resection and anastomosis irrespective of age unless it was precluded by poor bowel condition or haemodynamic instability, and the resection rate was high in both age groups. The results show that this operation could be performed in the elderly with a mortality rate and anastomotic leak rate comparable to those in younger patients. The anastomotic leak rate in the present patients was similar to the rate of 4–10 per cent reported in most other series[16–21]. Early surgical intervention was able to prevent death in patients with leakage, except for one who refused reoperation. The avoidance of a colostomy is particularly desirable in the elderly as they often have difficulty in self-care of the colostomy, which could significantly impair their independence. The elderly are also more prone to complications of colostomy[22]. Hartmann's procedure has been associated with a longer hospital stay and a high permanent colostomy rate of 60–90 per cent in reported studies[10,23]. In this series all of the elderly patients and nine of 13 younger patients had a permanent colostomy after Hartmann's procedure. Elderly patients often refused a second operation and there was also a reluctance among surgeons to perform reanastomosis in this group of high-risk patients. Reversal of Hartmann's procedure is associated with significant mortality and morbidity especially in the elderly[24].

Subtotal colectomy with ileocolic anastomosis has been shown to be a safe alternative to intraoperative lavage and primary colonic anastomosis[25,26], but which approach is better remains controversial. The only randomized trial showed no difference in mortality and morbidity rates but subtotal colectomy resulted in a significantly increased postoperative bowel frequency[21]. Segmental colectomy with intraoperative lavage was performed more frequently in the present patients but the authors consider these two approaches complementary. Subtotal colectomy was less favoured for the elderly as postoperative diarrhoea could be a serious problem especially in those with poor sphincter function, but it was mandatory in the presence of gangrenous proximal colon or caecum. This occurred more frequently in the elderly, probably related to their late presentation and more easily compromised blood supply. On the other hand, subtotal colectomy was preferred for young patients with more proximal lesions in order to decrease the chance of metachronous cancer in the future.

The mortality rate in this series for both younger patients and the elderly compares favourably with that of around 10 per cent in most series[10]. The mortality rate for the elderly was not significantly higher despite a higher incidence of premorbid risk factors and medical complications. Many reports have shown a higher mortality rate after emergency surgery in the elderly due to coexisting medical risk factors and decreased cardiopulmonary reserve[27,28]. However, improved perioperative care including better antibiotics, anaesthetic techniques, postoperative pain control, chest physiotherapy, ventilatory and inotropic supports has dramatically reduced deaths from cardiorespiratory complications in the elderly. The high frequency of ICU care and the longer postoperative hospital stay both reflect the special effort needed in the postoperative care of the elderly. Left-sided obstructing colorectal carcinoma is not a common encounter in the daily practice of a general surgeon and surgical management can be difficult[10,21]. The management of all the present patients by a specialist colorectal team certainly contributed to the outcome. This series represents a large experience of a colorectal team over a long period. A study[29] has shown that patients with a colorectal emergency are less likely to have a colostomy and have a lower mortality rate if managed by a specialist colorectal team. Finally, the authors believe that early operation after aggressive resuscitation is important in preventing death, as delay could result in perforation from caecal gangrene. A carefully performed preoperative flexible colonoscopy was useful in establishing the site and nature of the obstruction and excluding differential diagnoses such as pseudo-obstruction, hence allowing an early decision for laparotomy to be taken.

In conclusion, with improved perioperative care and management by a specialist colorectal team, emergency primary resection and anastomosis can be performed with favourable outcome and should be the treatment of choice in most elderly patients with left-sided obstructing colorectal carcinoma.

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Current surgical practice in screening for colorectal cancer based on family history criteria

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Background As awareness about colorectal cancer increases there has been a steady rise in the number of referrals of relatives of patients with colorectal cancer to colorectal surgeons for screening investigations based on family history criteria. Surgeons are generally not trained in either risk assessment of inherited colorectal cancer or genetic counselling. As this is a relatively new area of service, there is likely to be variation in the management of these individuals.

Methods This study investigated the family history criteria used and the colonic screening practices employed by a group of consultant colorectal surgeons by means of a postal questionnaire distributed and collected through their specialist association.

Results The results show not only wide variation in the practice of colorectal screening based on family history criteria, but also a considerable waste of resources in the provision of illogical and inappropriate investigations.

Conclusion Given the lack of evidence on which to base this clinical practice and the current financial difficulties in the health service, the authors question whether it is appropriate for surgeons to continue to provide such a service.

Colorectal cancer is the third commonest form of cancer and causes 17 000 deaths per year in England and Wales[1]. There is increasing awareness amongst relatives of patients with colorectal cancer that they may be 'at risk' for this disease, resulting in a rising demand from general practitioners for counselling services and investigation of such patients. Most of these referrals are directed to colorectal surgeons, placing additional strain on over-stretched outpatient clinics. Perhaps more worrying, most surgeons have little or no training in genetic counselling and the standard of advice given at such consultations is therefore uncertain.

As familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) account for approximately 2 per cent of all colorectal cancers, the majority of such tumours may be termed 'sporadic' and these have poorly defined inheritance patterns compared with FAP and HNPCC. The vast majority of referrals for screening based on family history criteria fall into this latter group but in these patients susceptibility to colorectal cancer is through genetic mutations which are currently unidentified[2]. As such screening is an evolving service with a limited evidence base, the provision of screening practices varies from one centre to another[3,4]. Furthermore, variation in screening practice can increase anxiety, particularly if one individual enters one regimen but a sibling in another city is investigated more intensively for no obvious reason.

To document current screening practices based on family history criteria among colorectal surgeons in England, a postal audit was conducted to determine how this service is currently provided and what intersurgeon variation exists.

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Materials and methods

The authors designed a postal questionnaire to address referral patterns for family history screening for colorectal cancer and current screening practices. The areas addressed in the questionnaire are listed in *Table 1*.

The questionnaire contained ten questions with up to five sections all requiring the participants to circle the most appropriate answers for their practice. The questionnaire was distributed to consultant surgeons in

Table 1 Topics addressed in the study questionnaire sent to consultant colorectal surgeons

- Referrals for colonic investigation based on family history criteria
  - Are the referrals appropriate?
  - Do you run a multidisciplinary clinic to see such referrals?
- Risk calculation based on family history criteria for colorectal cancer
  - Is it part of your practice?
- Do you use flexible sigmoidoscopy to investigate these patients?
  - If so, in whom and when?
- Do you use colonoscopy to investigate these patients?
  - What grades of staff perform these examinations and what is your completion rate?
- Do you use faecal occult blood tests to investigate these patients?
  - If so, in whom and when?
- Do you use barium enema to investigate these patients?
  - If so, in whom and when?
- How frequently do you repeat these investigations?
  - Annually, 3 yearly, 5 yearly
- At what age do you cease screening such patients?
  - >50, >60, >70, >80 years of age

For each topic a range of answers was provided and the respondents were asked to circle the response most appropriate to their practice

England, all of whom were members of the Association of Coloproctology of Great Britain and Ireland. Replies were collected anonymously at the Association's office and the responses compiled on a database using Excel (Microsoft, Seattle, Washington, USA) and SPSS for Windows (SPSS, Chicago, Illinois, USA).

Results

Of 160 questionnaires distributed, replies were obtained from 105 (66 per cent). In this survey 81 per cent of patients referred with a family history of colorectal cancer were seen in a surgical outpatient clinic. Only 25 per cent of surgeons liaise with clinical geneticists in the management of these patients, half through a combined surgical–genetics clinic and the remainder referred from a surgical to a genetics clinic.

Of patients referred for colonic screening based on family history criteria, one-third of respondents report that the general practitioners frequently refer inappropriately, usually because of a weak family history (i.e. risk similar to that of the general population).

However, 10 per cent of surgeons seeing patients for family history screening in their surgical clinic do not calculate an individual's risk of developing colorectal cancer based on the family history. Of the remaining surgeons, 28 per cent investigate all patients with a risk greater than one in 17 (i.e. with one first-degree family member affected by colorectal cancer). Whereas only 49 per cent of surgeons report that they investigate patients with a risk greater than one in 12 (one first- and one second-degree relative with colorectal cancer), all surgeons investigate those with a risk of greater than one in ten (a first-degree relative with colorectal cancer presenting at age 45 years or less (*Table 2*)).

Table 2 Surgeons' screening practices for colorectal cancer based on family history criteria

Question	Finding
Investigation of individuals with risk greater than	
1 in 17	28 per cent of surgeons
1 in 12	49 per cent of surgeons
1 in 10	100 per cent of surgeons
Modality of investigation	
Colonoscopy	97 per cent of surgeons
Completion rate for screening colonoscopies	>90 per cent claimed by 70 per cent of surgeons
Completion barium enema	28 per cent of surgeons do not perform such examinations
Barium enema	Preferred investigation for 3 per cent of surgeons
Flexible sigmoidoscopy	Used by 66 per cent of surgeons in 'low risk' cases; 33 per cent repeat 3–5 yearly
FOB testing	Used by 25 per cent of surgeons; 66 per cent in 'low risk' cases but almost all repeat annually
Frequency of repeat investigation	
After leaving a clean colon on the last occasion	12 per cent of surgeons repeat annually; 40 per cent repeat 3 yearly; 57 per cent repeat 5 yearly
Age of patients	
For cessation of screening	10 per cent of surgeons stop at 60 years; 81 per cent stop at 70 years; 10 per cent stop at 80 years

FOB, faecal occult blood

The preferred investigation for colonic screening on family history criteria is colonoscopy (*Table 2*). Such screening colonoscopies were undertaken by a combination of registrars and consultants in more than 70 per cent of the surveyed group. The completed colonoscopy rate is reported as being over 90 per cent for more than 70 per cent of the respondents. Barium enema was used by only 3 per cent of respondents as the primary investigation in this group of patients while 28 per cent of surgeons replied that they did not use barium enema examinations at all in this group. Only 72 per cent of surgeons perform a barium examination after an incomplete colonoscopy.

Some 66 per cent of surgeons undertaking colonic screening based on family history criteria use flexible sigmoidoscopy; this includes those who use flexible sigmoidoscopy as the sole investigation and those who use it in conjunction with either faecal occult blood (FOB) testing, barium enema or colonoscopy (*Table 2*). Some 20 per cent of surgeons use flexible sigmoidoscopy alone to investigate those in 'low risk' (one in 17 or one in 12) groups.

FOB testing is used by only 25 per cent of surgeons, of whom 90 per cent use these tests on an annual basis (*Table 2*).

Discussion

This study demonstrates large variations and some worrying inconsistencies in colonic screening practice based on family history criteria. Variation in screening practice is particularly undesirable as it causes anxiety among family members being cared for by different individuals. Although these variations and inconsistencies may be defended as this form of screening is an evolving practice, it also begs the question as to whether such screening is an appropriate use of resources.

Colorectal surgeons appear to receive the bulk of referrals requesting colonic screening for patients with a family history of colorectal cancer. The surgeons seeing these referrals report a significant number of inappropriate referrals with a weak family history, suggesting that general practitioners have a poor understanding of who should and should not be referred for this type of screening. The present study demonstrated that 80 per cent of referrals for colonic screening based on family history criteria are currently seen in the general surgical outpatient clinic. This may be inappropriate as this type of consultation may need to be protracted and it is often difficult to judge how much time to allow, particularly in the context of a busy outpatient clinic. Current practice may therefore be unfair on both patients and surgeons.

Although individuals found to be at 'low risk' for colorectal cancer based on family history criteria (including those whom surgeons may consider are referred inappropriately) do not require colonic investigation, many of these individuals are anxious about their health and are frequently investigated to allay this anxiety. It is uncertain whether there is therapeutic benefit in a surgical outpatient appointment for these individuals and even greater uncertainty about the relative risk to benefit of investigating this group.

Table 3 Inherited risk of developing colorectal cancer

	Lifetime risk of developing CRC[5]
Population risk	1 in 50
One first-degree relative with CRC	1 in 17
One first-degree relative and one second-degree relative with CRC	1 in 12
One first-degree relative aged under 45 years at diagnosis	1 in 10
Two first-degree relatives with CRC	1 in 6
Three first-degree relatives with CRC	1 in 2

First-degree relative is a sibling, parent or child; second-degree relative is an aunt, uncle, cousin or grandparent. CRC, colorectal cancer

It was alarming to find that 10 per cent of surgeons do not calculate risk for individuals based on their family history criteria (*Table 3*). This may reflect the lack of training and counselling skills, but also implies that these doctors may implement inappropriate management for these individuals and therefore should not be undertaking family history screening.

Concerns about the accuracy and frequency of colonoscopy are raised by some of the responses in this audit. Given the mixture of staff (registrars, clinical assistants and consultants) undertaking screening colonoscopies, a reported completion rate of over 90 per cent either reflects a very high standard of colonoscopy among the trainees and consultants or indicates that the estimates of complete colonoscopy are inaccurate. The authors suspect the latter explanation to be the case. Although colonoscopy is the investigation of choice in this group of patients, it is worrying that 28 per cent of surgeons do not use a barium enema in the event of incomplete colonoscopy. Given that there may be a preponderance of right-sided tumours in these patients, such lesions may be missed by incomplete colonoscopy, making a completion barium enema essential if there is doubt about whether the caecum has been visualized[6].

As FAP and HNPCC account for only 2 per cent of colorectal cancers, the majority of those referred for colonic screening based on family history criteria will have neither of these conditions and require less frequent colonic surveillance than those with either FAP or HNPCC. Although it may be reasonable to undertake colonoscopy in those with HNPCC at 2–3-year intervals[7], patients with less clearly inherited patterns of colorectal cancer almost certainly require less intensive surveillance. Unfortunately there is little evidence and much speculation on how these patients should be managed. Many of these patients are anxious about their cancer risk, and it is possible that many investigations are undertaken to allay such anxiety. The authors' experience is that such investigations are effective in allaying anxiety in the short term and should be discouraged. Despite this, 40 per cent of surgeons appear to be undertaking repeat colonoscopies yearly or every 2 years as part of their screening programmes. There is no justification for annual colonoscopy in screening based on family history criteria, particularly after leaving a clean colon on the previous examination. Whether follow-up should be every 3 or 5 years is a vexed question, but there is increasing evidence to support the longer interval between examinations particularly when small polyps (less than 0·5 cm) have been identified[9].

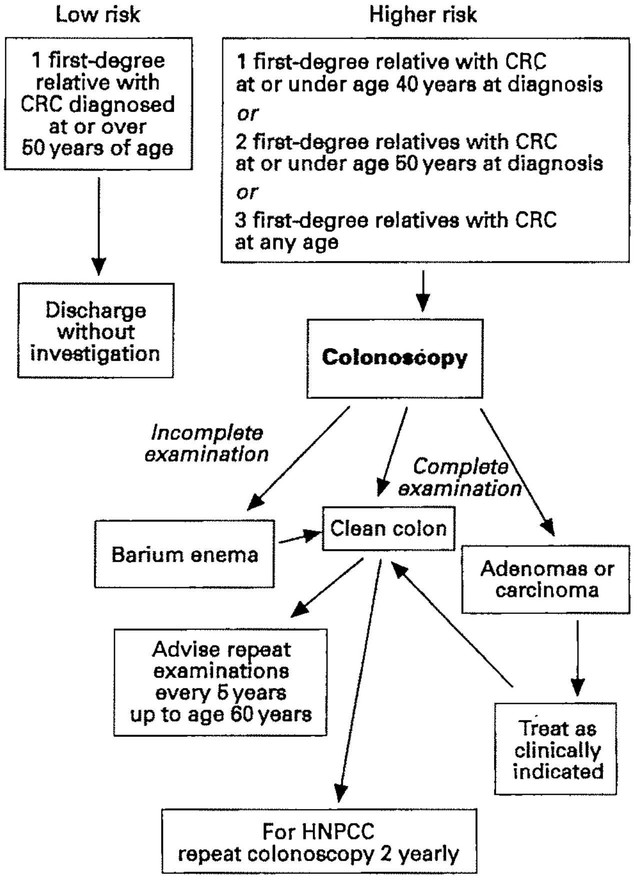
Low risk
Higher risk
1 first-degree relative with CRC diagnosed at or over 50 years of age
1 first-degree relative with CRC at or under age 40 years at diagnosis
or
2 first-degree relatives with CRC at or under age 50 years at diagnosis
or
3 first-degree relatives with CRC at any age
Discharge without investigation
Colonoscopy
Incomplete examination
Complete examination
Barium enema
Clean colon
Adenomas or carcinoma
Advise repeat examinations every 5 years up to age 60 years
Treat as clinically indicated
For HNPCC repeat colonoscopy 2 yearly

Fig. 1 A simplified scheme for the colonic investigation of patients with a family history of colorectal cancer (CRC). HNPCC, hereditary non-polyposis colorectal cancer

Complications of colonoscopy are fortunately rare, but with increasing numbers of colonoscopies carried out in an asymptomatic population the risk of colonoscopic perforation and occasional death becomes a significant concern[8]. The use of a combination of endoscopy and contrast enemas may help to reduce the risk of colonic perforation in asymptomatic patients. Close collaboration between endoscopy and radiology departments is required to achieve this on the same patient visit and thereby obviate the need for a second bowel preparation.

With the exception of patients with HNPCC, colonic screening based on family history criteria should probably cease at age 60 years as individuals over this age revert back to population risk for sporadic colorectal cancer. The cost of providing two or three further colonoscopies per patient for those aged over 60 years of age is considerable and could be more appropriately directed at symptomatic patients.

Although this survey did not address screening for familial cancer at other sites, the wide variation in colonic screening based on family history criteria is likely to reflect similar variation in the investigation of other inherited cancers. Given the limited resources of the health service, the wide variation in colonic screening based family history criteria demonstrated in this study raises serious questions about the appropriateness of surgeons conducting this type of screening as part of their outpatient practice. A solution to this problem may be to develop specific multidisciplinary clinics with clinical geneticists and nurse counsellors, who could see referrals for a large number of surgeons and feed back those requiring colonoscopy as appropriate. Clinical genetics departments are developing large computerized databases designed to recall patients at preset intervals; these could be used to organize appropriate colonoscopy for these patients. Such a development should provide a better service and reduce the number of unnecessary investigations.

Education of patients, general practitioners and surgeons is essential in developing a better service for this group of patients. Given that the evidence base for this type of activity is weak, a screening regimen is suggested in *Fig. 1*, based on the best evidence currently available from the USA[9,10] and the UK[11]. This may help surgeons to improve the selection of appropriate patients for colonic investigation and follow-up based on family history criteria.

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Preservation of pectoralis minor in axillary clearance for breast cancer

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Background There has been a gradual shift away from radical surgery towards conservation treatment for breast cancer. The pectoralis minor muscle is increasingly preserved in women undergoing axillary clearance as part of either breast conservation or mastectomy.

Methods A retrospective study was conducted to determine the axillary node count in 578 patients who underwent axillary clearance, 276 with removal of pectoralis minor and 302 who had the muscle preserved.

Results The mean number of nodes excised in the group who had pectoralis minor excised was 25·5 (range 8–50) compared with 24·5 (range 9–68) in the preservation group.

Conclusion For the majority of patients with operable breast cancer, retention of the pectoralis minor muscle is not associated with understaging or undertreatment of the axilla.

Axillary surgery is an intrinsic part of the staging and treatment of operable invasive breast cancer[1]. Recent studies have suggested that a minimum of ten negative nodes need to be sampled before the axilla can be deemed truly free from metastases[2,3]. The number of nodes examined also correlates significantly with the proportion of patients with heavy involvement, that is more than four positive nodes[4]. As part of the analysis of the European Organisation for Research and Treatment of Cancer trial 22881/10822, Ptaszynski *et al.*[4] found, of patients who had fewer than ten nodes removed, that 2 per cent had more than four nodes involved, rising to 3 per cent in those who had 11–15 nodes checked and 6 per cent in those who had more than 20 nodes removed. When axillary nodes are involved, clearance reduces both local relapse and mortality rates associated with the disease[2,5].

Nevertheless, axillary clearance does carry some short- and long-term morbidity, namely postoperative pain, arm lymphoedema and restriction of shoulder movement[6,7]. This latter complication may be reduced if the pectoralis minor muscle is not excised as part of the procedure. It is important to ensure that less extensive surgery does not lead to fewer nodes being removed so that nodal metastases are missed, with the result that the disease is understaged.

At Guy's Hospital Breast Unit axillary clearance is an intrinsic part of the surgery for operable invasive breast cancer. Originally, when the technique was performed as part of breast conservation, the pectoralis minor muscle was invariably sacrificed. With experience it was appreciated that the muscle could be retracted, without division of the nerve and blood supply, enabling a level III clearance. Since 1990 it has been usual to preserve the pectoralis muscle in patients having surgery for early breast cancer.

A review has been conducted of patients treated between 1982 and 1984, all of whom had the pectoralis muscle excised, and another group treated between 1992 and 1994, when the muscle was preserved. All specimens were processed in the Hedley Atkins laboratory by the same pathologists and during this time the technique of node harvesting did not change. The aim of the study was to determine the number of nodes removed and the proportion of positive nodes in the two groups.

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Patients and methods

The notes of 578 patients were reviewed. Some 276 were treated between 1982 and 1984, and had the pectoralis minor excised. The pathology of the axillary specimens was compared with that of those from 302 women who underwent surgery with preservation of the muscle between 1992 and 1994. All the patients had newly diagnosed unilateral breast cancer and underwent axillary clearance as part of either breast conservation therapy (combined with tumourectomy) or as an intrinsic component of modified radical mastectomy.

To enable the pathologist to establish the level of the nodes, specimens were marked at operation by the surgeon with catgut sutures. These were placed at the lower border of pectoralis minor and at the apex of the axilla. In women who did not have excision of pectoralis minor, another marker suture was placed on the fat next to the upper border of pectoralis minor. The fresh specimen was dissected in the pathology laboratory and the number of lymph nodes at each level was counted; representative samples were taken from each node after which the specimens were fixed, sectioned and stained with haematoxylin and eosin.

Table 1 Comparison of patients in the two treatment groups

	Pectoralis minor removed	Pectoralis minor retained
No. of patients	276	302
Age (years)*	56 (24–88)	56 (26–82)
Clinical tumour size*	2·7 (0–7·5)	2·5 (0–7)
≤2 cm†	103 (38)	132 (44)
>2≤5 cm†	160 (58)	151 (50)
>5 cm†	9 (3)	17 (6)
Unknown	4	2
Pathological node status†		
Node negative	150 (54)	157 (52)
Node positive		
1–3 nodes	72 (26)	99 (33)
4–9 nodes	27 (10)	30 (10)
≥10 nodes	27 (10)	16 (5)

*Values are mean (range); †values in parentheses are percentages

Table 2 Total number of nodes removed according to level of dissection

	Pectoralis minor removed			Pectoralis minor retained			
	Mean	Median	Range	Mean	Median	Range	P*
Total	25·5	25	8–50	24·5	23·5	9–68	0·10
Level I	14·8	14	0–31	15·4	15	0–55	0·17
Level II	6·6	6	0–24	5·2	5	0–15	0·0001
Level III	3·8	3	0–17	4·0	4	0–15	0·28

* χ^2 test

Results

Clinical details were similar in the 276 patients who had pectoralis minor removed and the 302 in whom the muscle was conserved (*Table 1*). Tumour size and type were also similar in the two groups. Additionally, there were similar proportions of tumour types in the two groups. Of the group who had the pectoralis minor excised, 54 per cent had histologically negative axillary nodes compared with 52 per cent of those who had the muscle preserved. When the node-positive patients were subdivided in terms of extent of involvement (1–3, 4–9 and 10 or more) there were similar proportions in both groups.

The mean total number of nodes removed in the two groups was similar: 25·5 in those who had the pectoralis minor excised and 24·5 in those in whom the muscle was retained (*Table 2*). There were similar numbers of nodes at level I in the two groups but significantly fewer at level II in patients who had pectoralis minor preserved. It is likely that this arose from the difficulty in marking accurately the upper border of pectoralis minor on the specimen. Similar numbers of nodes were found at level III.

Discussion

These results suggest that retention of the pectoralis minor muscle does not result in a significant fall in the number of nodes excised. It is thus unlikely to lead either to understaging of the disease or an increased risk of axillary recurrence. This agrees with a previous study from Milan which compared results after resection and preservation of pectoralis minor in women undergoing breast conservation therapy[8]. If this approach is adopted, it is important to palpate the interpectoral (Rotter's) nodes during operation since these may be involved in up to 21 per cent of patients[9].

Conserving the pectoralis minor muscle lessens both immediate postoperative pain and also both pain and shoulder dysfunction 6 months after surgery[10]. Long-term atrophy of pectoralis major may be reduced from 54 to 6 per cent. As part of the reduction in morbidity of breast surgery, preservation of the pectoralis minor muscle during axillary clearance does not appear to carry any penalty, either in staging or treatment.

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Tissue markers as predictors of postoperative adhesions

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Background Postoperative adhesion formation has been associated with a decreased capacity to degrade intra-abdominally deposited fibrin. Adhesions, once lysed, have a high propensity for reformation. This study tested the hypothesis that patients with a high propensity for adhesion formation as well as adhesion tissue had a reduced fibrinolytic capacity.

Methods Peritoneal biopsies were taken during abdominal surgery from 21 patients who had previously undergone operation; previously formed adhesion tissue was sampled from ten of these patients. Adhesion formation was scored. The fibrinolytic capacity of peritoneum was determined in tissue extracts.

Results At the time of opening of the abdominal cavity, levels of plasminogen activator inhibitor (PAI) type 1 ($P = 0{\cdot}009$) and tissue-type plasminogen activator (tPA)/PAI complex ($P = 0{\cdot}008$) were increased in peritoneal samples from patients with severe adhesions compared with those in samples from patients with less severe adhesions. Adhesion tissue similarly had reduced fibrinolytic capacity as judged by a decrease in tPA activity ($P = 0{\cdot}005$) and an increase in PAI-1 level ($P = 0{\cdot}01$), reflected in an increased level of tPA/PAI complex ($P = 0{\cdot}008$) compared with unaffected peritoneum.

Conclusion These observations demonstrate reduced fibrinolytic capacity in peritoneal tissue in patients with a greater propensity for development of adhesions and likewise in adhesion tissue. This suggests that components of the fibrinolytic system may be used as markers of an increased risk of adhesion development.

Postoperative adhesions are an important and so far unsolved surgical problem. Recent observations indicate that 93–100 per cent of patients who have undergone abdominal surgery develop adhesions[1,2], some of whom will later develop bowel obstruction. The risk of developing bowel obstruction after operation ranges from 0·3 to 10·7 per cent[1,3–5], rising to 22 per cent if concomitant radiotherapy has been given[6].

Postsurgical adhesions are the predominant cause of small bowel obstruction, accounting for approximately 70–80 per cent of cases[1,7,8], often associated with high morbidity and mortality rates[7,8].

There is a vast body of evidence from experimental animal studies indicating that peritoneal fibrinolytic capacity is crucial in the early formation of adhesions[9–11], but it is not completely clear whether or not this is relevant to humans. Fibrinolysis is accomplished by the activation of plasminogen to plasmin, an enzyme with a broad proteolytic range. In humans local peritoneal plasminogen activation has been explored to some extent; it has been shown that peritoneal plasminogen activation is decreased during surgery[12] and in peritonitis[12,13], conditions associated with subsequent adhesion formation.

Adhesions, once divided, tend to reform[14], and this seems to translate into an increased morbidity rate with a high frequency of relapse of bowel obstruction once adhesiolysis has been performed[1]. Adhesion tissue seems to have a typically high propensity for development of adhesions, hypothetically because of a reduced ability to degrade fibrin deposits.

Clinically it is well known that some patients seem to have an high aptitude for extensive adhesion formation. However, the reason for this is poorly understood. Because a reduced fibrin degradation capacity has been associated with adhesion formation it was hypothesized that these individuals have reduced peritoneal plasminogen activation.

The aims of this study were to investigate if adhesion tissue has reduced plasminogen activation compared with peritoneum, and if patients who have developed extensive adhesions have reduced peritoneal plasminogen activation compared with others.

Patients and methods

Patients

Peritoneal biopsies and plasma samples were taken from 21 patients undergoing abdominal surgery. All patients had previously undergone abdominal surgery. The most common previous operations were appendicectomy, cholecystectomy and gynaecological operations, and some had been operated on for bowel obstruction. The time lapse from the first operation varied from 1 to 28 years. The present indications for operation were mainly colonic and gastric resections. In three patients the present indication was bowel obstruction. There were nine men and 12 women of mean age 66 (range 37–88) years. Patients with signs of intra-abdominal infection, disseminated cancer or peritoneal carcinosis were excluded. The time taken to perform the surgery was recorded. The study was approved by the local ethics committee.

Adhesion formation

At surgery adhesion formation was scored into three different categories based on their quantity, quality and extent in relation to previous surgery. The aim of the categorization was to

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Table 1

	Quantity of adhesions		Quality of adhesions		
	To the site	Extensive	Filmy	Dense	Risk of damage
Group 0	–	–	–	–	–
Group I	+	–	+	–	–
Group II	+	+	+	+	+

distinguish patients with severe adhesion formation from those who did not. The classification is detailed in *Table 1*.

Plasma samples

Blood and peritoneum were sampled simultaneously at the time of opening and closure of the abdominal cavity. Venous blood was collected without stasis into three different tubes to optimize analysis of individual factors[15,16]. Blood samples were immediately put on ice and centrifuged (4°C at 10 000*g*). The supernatant was aliquoted and stored at – 70°C.

Peritoneal samples

Immediately after opening and before closing the abdominal cavity biopsies of parietal peritoneum were taken close to the incision. In ten patients it was possible to isolate and sample previously formed adhesion tissue. In such patients the adhesions were divided as in routine adhesiolysis and samples were taken from these sites. Adhesion samples were taken at the beginning of the operation. All biopsies were quickly rinsed in saline solution, put in an airtight tube and snap frozen. The biopsies were then stored at – 70°C until further processed.

Tissue homogenization and extraction

Previous experiments had demonstrated that 40–60 mg tissue was sufficient[17]. The sample was rinsed in buffer consisting of phosphate-buffered saline (PBS) with sodium chloride 0·5 mol/l, pH 7·4, blotted, cut into smaller pieces and transferred to a test tube, to which was added ice-cold homogenizing buffer to a final concentration of 40 mg tissue per ml buffer. This buffer consisted of PBS with sodium chloride 0·5 mol/l and 0·01 per cent Triton X-100. The sample was homogenized over 1 min using an Ultra Turrax homogenizer (Janke and Kunkel, Staufen, Germany). The homogenate was centrifuged at 4°C for 3 min at 10 000*g*; the supernatant was withdrawn and stored in aliquots at – 70°C until analysed in batches. Results were normalized to wet weight which previously has been demonstrated to be comparable to normalizing to total protein concentration or to DNA[17].

Biochemical assays

The fibrinolytic components were determined similarly in plasma and tissue extracts. Total antigen levels of tissue-type plasminogen activator (tPA), urokinase plasminogen activator (uPA) and the main inhibitor, plasminogen activator inhibitor (PAI) type 1, were analysed by enzyme-linked immunosorbent assay, using commercially available kits (Biopool, Umeå, Sweden).

PAI-1 inhibits fibrin degradation by forming an inactive complex between plasminogen activators (tPA/PAI complex). The plasminogen activator functional capacity (tPA activity) as well as the tPA/PAI complex was measured with commercial kits (Novo Nordisk, Bagsvaerd, Denmark).

Statistical analysis

Values are median (interquartile range). Non-parametric tests were used, the Mann–Whitney *U* test for analysing differences between groups of patients and the paired Wilcoxon signed rank test for analysing differences in the same patient. $P < 0.05$ was considered significant.

Results

Adhesion formation

All patients had developed adhesions and none was categorized into group 0. Thirteen patients were categorized in group I and eight in group II, three of whom had previously had surgery because of bowel obstruction due to adhesions. There was no significant difference in time lapse from the first abdominal operation to the present between groups I and II. In three patients categorized in group II, the present indication for surgery was adhesive bowel obstruction. Men and women were equally distributed between the groups. The mean time taken for surgery was longer for patients in group II: 2·8 (range 0·6–4·0) h compared with 2·2 (range 0·9–3·4) h for those in group I ($P = 0{\cdot}14$).

Adhesion tissue compared with peritoneum

Plasminogen activators. Tissue expression of components of the plasmin system in parietal peritoneal samples from the beginning of surgery was compared with that of adhesion tissue from the same patient. In the adhesion tissue tPA activity was less than 30 per cent of that in adjacent peritoneum ($P = 0{\cdot}005$). In contrast, the level of uPA antigen was fivefold higher in adhesion tissue compared with peritoneum ($P = 0{\cdot}008$) (*Fig. 1*).

Plasminogen activator inhibitors. The level of PAI-1 was sixfold higher in adhesion tissue compared with peritoneum ($P = 0{\cdot}01$). The increased PAI-1 expression resulted in correspondingly raised levels of tPA/PAI complex in adhesions compared with peritoneal biopsies ($P = 0{\cdot}008$), reflecting a quenching of tPA (*Fig. 2*).

Severe compared with less severe adhesion formation

Plasminogen activators. There were no significant differences in tPA activity between patients in group I and those in group II at the beginning ($P = 0{\cdot}18$) or at the end ($P = 0{\cdot}07$) of surgery. Nor were there any differences in the expression of uPA antigen between the groups at the beginning ($P = 0{\cdot}3$) or end ($P = 0{\cdot}08$). Tissue levels are depicted in *Fig. 3*.

Plasminogen activator inhibitors. In contrast, the level of PAI-1 was significantly higher both at the beginning ($P = 0{\cdot}009$) and at the end ($P = 0{\cdot}04$) of the operation in group II compared with group I (*Fig. 4*). There was also a significant difference in the level of tPA/PAI complex both at the beginning ($P = 0{\cdot}008$) and at the end ($P = 0{\cdot}01$) of the operation.

Intraoperative changes

Plasminogen activators. Intraoperative changes in fibrinolytic components were investigated by comparing tissue samples from the beginning with those obtained at the end of surgery. The tPA activity was significantly reduced during the operation in group I ($P = 0\cdot01$) as well as in group II ($P = 0\cdot002$). There was no significant change in the level of uPA antigen during the operation in either group (group I, $P = 0\cdot1$; group II, $P = 0\cdot06$) (*Fig. 3*).

Plasminogen activator inhibitors. During surgery the PAI-1 level displayed a diverging path in the two groups, increasing in group I ($P = 0\cdot04$) and declining slightly in group II ($P = 0\cdot03$). Levels of the tPA/PAI complex increased in both group I ($P = 0\cdot004$) and in group II ($P = 0\cdot005$) (*Fig. 4*).

Systemic expression

There was no significant difference in plasma levels of plasminogen activators, measured as tPA activity, tPA antigen and uPA antigen, between the two groups either at the beginning ($P = 0\cdot3$, $P = 0\cdot7$ and $P = 0\cdot9$ respectively) or at the end ($P = 0\cdot4$, $P = 0\cdot2$ and $P = 0\cdot8$ respectively) of operation. Nor did the systemic levels of plasminogen inhibitor PAI-1 (beginning, $P = 0\cdot9$; end, $P = 0\cdot3$) or tPA/

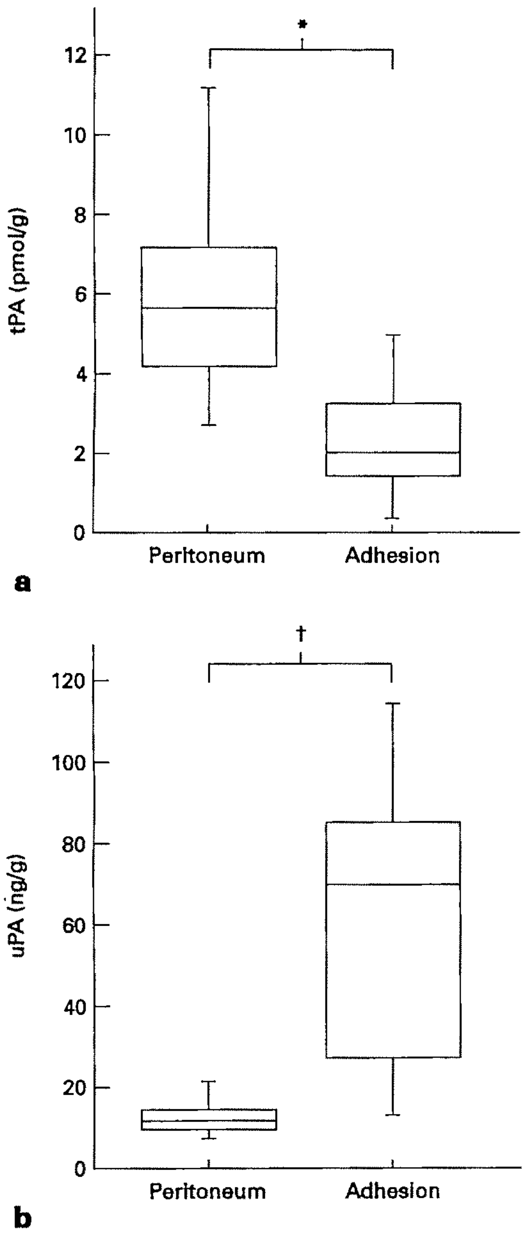

Fig. 1 Expression of **a** tissue-type plasminogen activator (tPA) and **b** urokinase plasminogen activator (uPA) in adhesion tissue and peritoneum from the same patients. Values are median (horizontal bars), with interquartile range (boxes) and 10–90th centile (error bars). $*P = 0\cdot005$, $\dagger P = 0\cdot008$ (Wilcoxon signed rank test)

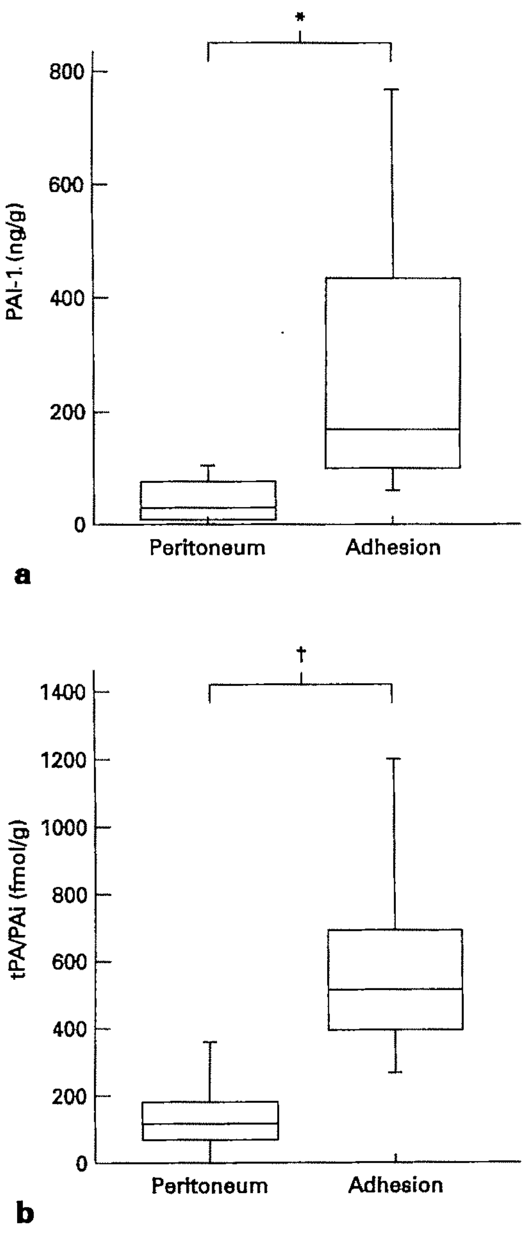

Fig. 2 Expression of **a** plasminogen activator inhibitor (PAI) type 1 and **b** tissue-type plasminogen activator (tPA)/PAI complex in adhesion tissue and peritoneum from the same patients. Values are median (horizontal bars), with interquartile range (boxes) and 10–90th centile (error bars). $*P = 0\cdot01$, $\dagger P = 0\cdot008$ (Wilcoxon signed rank test)

PAI complex (beginning, $P=0{\cdot}7$; end, $P=0{\cdot}6$) differ significantly between the two groups.

Discussion

The present observations indicate that postoperative adhesions have a reduced potential to degrade fibrin, mainly because of an increased expression of PAI-1, and that individuals with an increased propensity for development of extensive adhesions likewise seem to have a reduced peritoneal capacity to degrade fibrin, primarily owing to an overexpression of PAI-1. These results suggest that components of the plasmin system, particularly PAI-1, could be used as tissue markers of the propensity for development of extensive adhesions after surgery.

The question of which specific part of the adhesion is important has arisen. One possibility is to sample at the attachment site, a location that may be of interest in the pathogenesis of adhesions. However, because the cellular and molecular events that contribute to the formation of

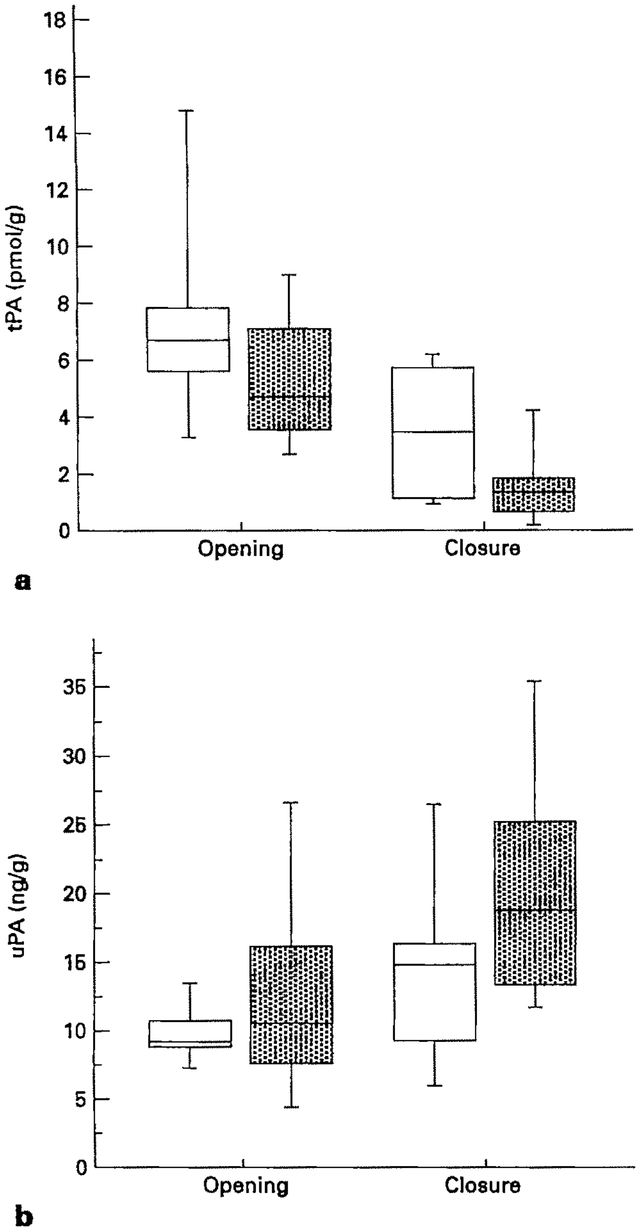

Fig. 3 Expression of a tissue-type plasminogen activator (tPA) and b urokinase plasminogen activator (uPA) in peritoneal samples taken at the start and end of operation from patients with less severe adhesions (group I; open boxes) and those with more severe adhesions (group II; filled boxes). Values are median (horizontal bars), with interquartile range (boxes) and 10–90th centile (error bars). There were no significant differences between the two groups at either time point (Mann–Whitney *U* test)

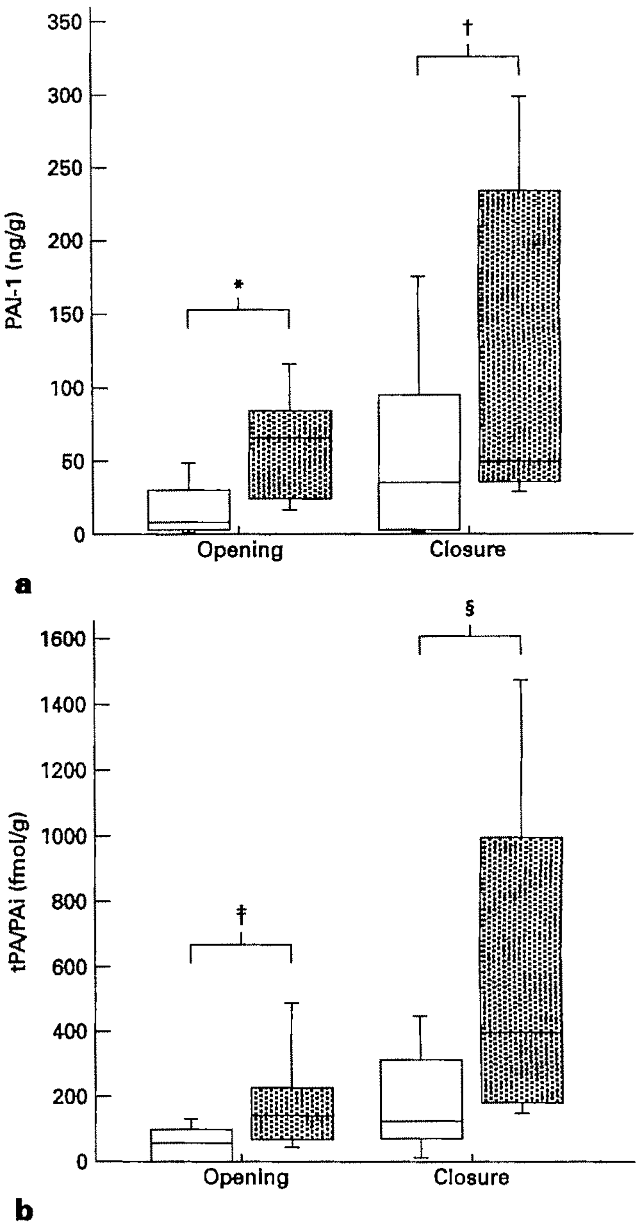

Fig. 4 Expression of a plasminogen activator inhibitor (PAI) type 1 and b tissue-type plasminogen activator (tPA)/PAI complex in peritoneal samples taken at the start and end of operation from patients with less severe adhesions (group I; open boxes) and those with more severe adhesions (group II; filled boxes). Values are median (horizontal bars), with interquartile range (boxes) and 10–90th centile (error bars). $^*P=0{\cdot}009$, $^{\dagger}P=0{\cdot}04$, $^{\ddagger}P=0{\cdot}008$, $^{\S}P=0{\cdot}01$ (Mann–Whitney *U* test)

adhesions are believed to occur during the first few days after surgery, and the time lapse since the last operation could be several years in the present patients, the attachment site was not sampled. Instead the adhesions were divided in routine fashion and sampled from the divided ends, which represent a site where adhesions typically reform[18].

Adhesion tissue had decreased tPA activity, a finding not reported previously. However, decreased peritoneal tPA activity has been observed in conditions associated with increased adhesion formation in humans[2,12,19]. Moreover, pharmacologically induced inhibition of fibrinolysis in animals after surgery increased adhesion formation[17]. It therefore seems reasonable to assume that the reduced tPA activity observed in adhesion tissue may explain the high frequency of reformation after lysis. A possible explanation for the reduced tPA activity is an overexpression of PAI-1, which quenches t-PA, as observed in the present study. PAI-1 may be produced by a variety of cells including fibroblasts[20] and mesothelium, and is deposited in the submesothelial matrix where it partly co-localizes with macrophages[21]. A possible source of PAI-1 may therefore be the mesothelial cells and, particularly in adhesion tissue, PAI-1 depositions produced by fibroblasts and macrophages in the extracellular matrix.

The high levels of uPA in adhesion tissue were unexpected. uPA has been more associated with tissue remodelling than fibrin degradation[22], and the overexpression of uPA in adhesion tissue may reflect that adhesions represent an active, dynamic tissue in remodelling rather than profibrinolytic activity. tPA is more fibrin specific[23], the main activator in peritoneum[12], and may therefore have a greater impact on fibrin degradation in the peritoneal cavity than uPA.

PAI-1 inhibits fibrin degradation by forming inactive complexes with plasminogen activators. That this actually occurred in peritoneal tissue was demonstrated by the identification of tPA/PAI complexes and covariance in the levels of PAI-1 and tPA/PAI complex. Peritoneal PAI-1 levels were tenfold higher in patients with an increased propensity for development of adhesions, and six times greater in adhesion tissue compared with adjacent, unaffected peritoneum. None of the patients with less severe adhesion formation had a PAI-1 level exceeding 60 ng/g, whereas seven of eight patients with severe adhesions had. Thus if the cut-off level was set to 60 ng/g, the majority of those at a greater risk would be identified. Systemically, there were no significant differences between patients with varying propensity to form adhesions, and peripheral blood samples seem not to be useful in identifying patients at high risk for extensive adhesions.

The present findings may explain why adhesions are prone to reform and why some individuals are at high risk of forming adhesions. They also suggest that components of the plasmin system, particularly PAI-1, could be used as tissue markers of the propensity to develop adhesions after surgery and may have potential for identification of high-risk patients who would benefit from adjuvant therapy. In addition to the potential direct clinical value, these observations could be useful in understanding the biology of adhesion formation and in developing new therapeutic approaches. Theoretically, it may be possible to reduce adhesion formation, by inhibiting the plasminogen inhibitor PAI-1 locally.

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Erratum

Please note that page numbers given on the spine of the August 1998 issue (85:8) were incorrect. The correct page numbers for this issue are 1025-1168.

British Journal of Surgery 1998, 85, 1555–1593

Surgical Research Society Abstracts

The following abstracts were presented at the 88th meeting of the Surgical Research Society. The meeting was organized by and held at the Royal College of Surgeons of Ireland on 2–3 July 1998. One hundred and fifteen papers were presented during the scientific sessions. The Patey Prize was awarded to Miss D. McNamara for her paper entitled 'Tamoxifen is anti-angiogenic *in vitro* and attenuates vascular endothelial growth factor-mediated angiogenesis *in vivo* without adverse effects on wound healing'.

Increased TNF-α2 microsatellite allele frequency in Barrett's adenocarcinoma

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Background Tumour necrosis factor (TNF) is a key modulator of the host inflammatory response and may be important in tumorigenesis and progression. It has been demonstrated that the microsatellite allele TNFa2 (associated with a high level of TNF secretion) is markedly over-represented in patients with colorectal cancer. The relationship between TNFa2 allele frequency and tumour site and type was determined in patients with gastro-oesophageal malignancy.

Methods Some 177 Caucasian patients with histologically confirmed gastro-oesophageal malignancy and 180 controls from the regional tissue typing centre were studied. Genomic DNA was extracted from peripheral blood monocytes and the locus containing the TNFa polymorphic marker was amplified using the polymerase chain reaction. The TNFa alleles for each individual were then resolved on a 6 per cent denaturing acrylamide gel containing urea $7{\cdot}65\ \text{mol}\ \text{l}^{-1}$. The Monte Carlo simulation was used to compare the distribution of TNFa alleles in different tumour types and sites. When relevant, individual alleles were compared using a $2 \times 2\ \chi^2$ test.

Results The 177 patients were divided into three main groups: squamous carcinoma of the oesophagus (42), adenocarcinoma arising at the gastro-oesophageal junction or oesophagus, i.e. Barrett's adenocarcinoma (56) and adenocarcinoma of the stomach (79). The TNFa allele frequency profile of patients with Barrett's adenocarcinoma differed significantly from that of the control population ($P < 0{\cdot}008$). This difference was due to over-representation of the TNFa2 allele in these patients compared with controls (39 *versus* 24 per cent respectively; $P < 0{\cdot}0001$). No significant differences were noted in the TNFa allele frequency profile in patients with either squamous carcinoma of the oesophagus or distal adenocarcinoma of the stomach compared with controls. In particular the TNFa2 allele was present in 28 and 29 per cent respectively.

Conclusion Increased TNFa2 microsatellite allele frequency is present in Barrett's adenocarcinoma. This study demonstrates that gene loci within or close to the TNF locus may be important in oesophageal carcinogenesis. The results suggest that further study of the highly polymorphic TNFa locus may contribute to the understanding of the molecular aetiology of Barrett's adenocarcinoma.

p53 and *p16* gene therapy results in killing of pancreatic cancer cells

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Background Pancreatic cancer displays high levels of loss of function of tumour suppressor genes *p53* (75 per cent) and *p16* (80 per cent), which have a major role in cell cycle control. *p16* prevents the hyperphosphorylation of retinoblastoma protein (pRb) thereby promoting G1 arrest. *p53* also has a major role in *p53*-dependent apoptosis. The aim of this study was to replace wild-type *p53* and *p16* into pancreatic cancer cells and assess the effects on cell growth and cell death.

Methods Human pancreatic cancer cell lines BxPc3, MIAPACA, Pancl (all homozygously deleted for *p16* and loss of heterozygosity *p53*), CFPAC1 (wild-type *p16*) were used. The cell lines Hep2, SW620 and FF1 (wild-type *p53* and *p16*) were also used. Gene transfer was achieved using adenovirus expressing wild-type *p53* and *p16* and infection was carried out at a multiplicity of infection of 50–100. Control infections were carried out using adenovirus expressing β-galactosidase. Expression of therapeutic genes was confirmed using polymerase chain reaction (PCR), reverse transcription–PCR, Western blotting and immunofluorescence. Cell growth curves were plotted for 7 days following gene transfer and were performed in triplicate ($n = 3 + 3$). Cell cycle distribution was assessed using flow cytometry. The presence of apoptosis was confirmed using DNA laddering and quantified by TUNEL assay. Expression of pRb was assessed by Western blotting.

Results The transfer of wild-type *p53* inhibited cell proliferation by 78–91 per cent and the transfer of wild-type *p16* inhibited cell proliferation by 66–83 per cent with respect to β-galactosidase controls. The transfer of *p16* induced G1 arrest in all cell lines. Following transfer of *p53* the apoptosis index was significantly increased ($P < 0{\cdot}004$, Mann–Whitney *U* test) compared with control infection. *p16* also resulted in increased apoptosis ($P < 0{\cdot}03$). Transfer of wild-type *p16* was shown to be associated with downregulation of pRb.

Conclusion Adenoviral-mediated transfer of wild-type *p53* and *p16* resulted in significant growth inhibition and increased rates of apoptosis in human pancreatic cancer cells. These results indicate a new approach to the therapy of pancreatic cancer.

Differential gene expression in adenocarcinoma of the oesophagus

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Background Current knowledge of the genetic changes in the genesis of adenocarcinoma of the oesophagus is limited to only a few candidate genes. From the Human Genome Mapping Project, an increasing number of genes have been identified and assigned to functional pathways. Many of these govern cellular proliferation and morphology and their derangement may be implicated in tumour development. Genes that may have a role in tumorigenesis were examined systematically by generating, on a large scale, expression profiles in oesophageal adenocarcinoma.

Methods Messenger RNA was extracted from 18 adenocarcinomas, matched normal tissue and five metaplastic/dysplastic samples. Reverse transcribed complementary DNA (cDNA) was plated in duplicate into a 96-well format and uniform amplification of this panel was established by semiquantitative polymerase chain reaction (PCR) with eight housekeeping genes. Some 224 primers for nine pathways were designed to amplify to the same conditions and optimized across two human cDNA panels before profiling.

Results PCR expression profiles were generated from 159 genes of which 32 demonstrated differential expression in at least 50 per cent of tumours compared with normal tissue and 12 of these in over 70 per cent of oesophageal adenocarcinomas.

Gene group	Downregulated genes	Upregulated genes	Gene group
Cytoskeletal	Cytokeratin 4	Cyclin E	Cell cycle
	Cytokeratin 15	Aminopeptidase	GI specific
Microbutule	Mitotic kinesin-like protein	Hepatic nuclear factor 1	
	Microtubule-associated protein Tau	Platelet-derived growth factor α	Growth factor
	Restin filament-associated protein	Tumour necrosis factor receptor 1	Cytokine
Oncogene	Retinoic acid-binding protein	Wnt integration site	Wingless/cell adhesion

Conclusion Through systematic expression profiling, numerous genes have been shown to have altered transcription levels in oesophageal adenocarcinoma and may be potential targets in the elucidation of biomarkers of malignant risk or poor prognosis.

Tamoxifen is antiangiogenic *in vitro* and attenuates vascular endothelial growth factor-mediated angiogenesis *in vivo* without adverse effects on wound healing

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Background Tumour growth is angiogenesis dependent. The authors have previously shown that surgery results in a permissive environment for angiogenesis, mediated in part by vascular endothelial growth factor (VEGF). Surgery may paradoxically promote the growth of micrometastases associated with gastrointestinal and other solid tumours. The use of antiangiogenic strategies in the perioperative period may reduce tumour recurrence. However, concerns that antiangiogenic agents may impair wound healing and compromise gastrointestinal anastomotic integrity must be addressed. Tamoxifen reduces serum levels of VEGF in patients with cancer and may therefore inhibit VEGF-mediated angiogenesis. The effect of tamoxifen on angiogenesis was evaluated and the effects of its perioperative use on wound and anastomotic healing was assessed.

Methods *In vitro* proliferation of human microvessel endothelial cells (HMECs) and umbilical vein endothelial cells (HUVECs) treated with tamoxifen (100 ng ml^{-1}–2·5 mg ml^{-1}) or vehicle was assessed. Proliferation was quantified using 5-bromo-2′-deoxyxuridine labelling. The *in vivo* effects of tamoxifen on angiogenesis were assessed in adult male Sprague–Dawley rats pretreated with tamoxifen or placebo for 3 days, injected with VEGF-impregnated Matrigel and then treated for a further 5 days. Microvessel density within the gel was quantified. The effect of tamoxifen on wound healing following laparotomy and small bowel anastomosis was studied on animals pretreated with tamoxifen or placebo for 3 days. Therapy was continued for up to 10 days after operation at which time animals were killed and laparotomy wounds and gastrointestinal anastomoses were assessed.

Results HMEC, but not HUVEC, proliferation was attenuated by tamoxifen ($P = 0{\cdot}001$). Microvessel density in tamoxifen-treated gels was decreased compared with that in controls (mean(s.e.) 44·9(5·6) *versus* 65·3(6·5) per high-powered field; $P < 0{\cdot}05$). Endothelial cell migration *in vivo* was significantly reduced by systemic tamoxifen (23·2(3·5) *versus* 43·8(6·0); $P < 0{\cdot}02$). There was no difference in macroscopic indices of wound healing, including wound breakdown, anastomotic dehiscence, adhesion score or survival, between the two groups (χ^2 test).

Conclusion In summary, tamoxifen is antiangiogenic *in vitro* and attenuates VEGF-mediated angiogenesis *in vivo* without adversely affecting wound healing or anastomotic integrity. Further evaluation to assess the value of neoadjuvant tamoxifen in dormancy therapy of micrometastases in the perioperative period is warranted.

Clinical outcome of patients with advanced colorectal cancer treated with the antigastrin immunogen, Gastrimmune

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Background Gastrin is a potent growth factor for colorectal cancer, acting both by endocrine and autocrine routes. Gastrimmune is an immunogenic formulation of a gastrin-17:diptheria toxoid conjugate that induces high-affinity neutralizing antibodies to amidated and glycine-extended gastrin-17. Neutralization of these gastrin forms following vaccination with Gastrimmune has been shown to extend survival in animal models of colorectal cancer. The safety, tolerance and the accumulated survival data from patients with advanced colorectal cancer, who participated in the initial studies of Gastrimmune, was assessed.

Methods Some 40 patients received Gastrimmune therapy; 77 patients were recruited to the placebo arm of an immunotherapy study (Cancer Research Campaign data) performed concurrently at the same centre. There were matching inclusion and exclusion criteria. Patients received three injections of Gastrimmune at weeks 0, 4 and 8; control patients similarly received three immunizations.

Results No systemic symptoms were attributable to Gastrimmune; adverse effects were limited to the injection site. There were no significant differences in baseline demographic variables between the two groups with the exception of sex ratio (29 of 40 males in Gastrimmune group, 52 per cent control) and the presence of liver metastases (35 of 40 *versus* 65 per cent, respectively). The median survival in Gastrimmune and placebo groups from study entry was 338 and 184 days respectively. The difference was significant on univariate analysis ($P = 0{\cdot}046$, log rank test). Statistical significance was maintained following multivariate analysis, adjusted for age, sex, lung and liver metastases, radiotherapy and chemotherapy (risk ratio 0·61 (0·36–0·99), $P = 0{\cdot}026$, Cox regression).

Conclusion Gastrimmune immunization appears to be safe and well tolerated, and may result in a survival advantage for patients with advanced colorectal cancer.

Potential for reducing micrometastatic load by inducing apoptosis in colorectal cancer

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Background Evidence is emerging to suggest that, despite undergoing 'curative' surgery, many patients with colorectal cancer have a demonstrable micrometastatic tumour load. Present chemotherapeutic regimens for colorectal cancer are aimed at interrupting DNA synthesis (karyokinesis). This limitation to a single phase of the cell cycle permits micrometastatic 'escape'. Cytoskeletal remodelling during another phase of the cycle is necessary for cellular cleaving to complete mitosis (cytokinesis). The effects of Jasplakinolide, a novel cyclic peptide isolated from a marine sponge that polymerizes F-actin microfilaments (Kd = 50 nM), on colon cancer cells *in vitro* are presented.

Methods The effect of Jasplakinolide on growth of the colonic carcinoma cell line T84 was examined *in vitro*. Cell population growth was quantified with a tetrazolium salt-based colorimetric assay (MTT). DNA replication activity was measured in terms of the incorporation of radiolabelled [^{3}H]thymidine. Cells were maintained in log-phase culture at 37°C and seeded at a density of 3×10^5 per well in 96-well plates. Complete medium was removed at 24 h and replaced with fresh medium containing Jasplakinolide 1–250 nmol l^{-1} or its vehicle (no effect shown). Cellular morphology was assessed with confocal laser scanning microscopy. Apoptosis was measured by flow cytometry (propidium iodide). All results are for Jasplakinolide 50 nmol l^{-1} ($n = 6$).
Results Jasplakinolide had a cytostatic effect on colon cancer cells over a period of 48 h (mean(s.d.) absorbance 0·30(0·47); control 1·56(0·95); $P < 0{\cdot}001$; *t* test). No statistical difference in [^{3}H]thymidine incorporation between control (10 279·2(203·8)) and experimental populations (10 182·9(251·1)) was observed over this time ($P > 0{\cdot}5$). Cells developed a strikingly deranged morphology with enlarged, multilobular nuclei suggesting dissociation between karyokinesis and cytokinesis. The apoptotic rate of colon cancer cells was dramatically increased by Jasplakinolide (more than 85 per cent apoptosis at 72 h, $P < 0{\cdot}001$).
Conclusion These data indicate that inhibition of colonic cancer growth *in vitro* can be achieved by targeting the cytoskeletal microfilaments. Jasplakinolide has a cytostatic effect on colon cancer cells without affecting DNA synthesis (cell-cycle specificity). This offers a potential approach in the treatment of colorectal cancer, raises the possibility of chemotherapeutic synergy and may provide the basis for preventing micrometastatic invasion.

Targeting prostaglandin E$_2$ for the medical treatment of aortic aneurysms

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Background Loss of medial smooth muscle and inflammation are important features of abdominal aortic aneurysm (AAA). Cyclo-oxygenase 2 in adventitial macrophages synthesizes prostaglandin E$_2$ (PGE$_2$) which may stimulate the synthesis of other inflammatory mediators including interleukin (IL) 6. The effects of indomethacin on the secretory products of short-term explant cultures of human AAA biopsies were investigated.
Methods Secretion of PGE$_2$, matrix metalloproteinase (MMP) 9 and the cytokines IL-6 and monocyte chemotactic protein (MCP) 1 into conditioned media of AAA explant cultures was measured by immunoassay. 5-Bromo-2′-deoxyuridine uptake was used to investigate the influence of PGE$_2$ on DNA synthesis of smooth muscle cells cultured from AAA biopsies.
Results

Conditioned media at 96 h	Control	Indomethacin 10 µmol l^{-1}	*P**
MMP-9 (ng ml^{-1}) ($n = 4$)	12(2)	22(3)	n.s.
MCP-1 (ng ml^{-1}) ($n = 6$)	73(51)	41(17)	n.s.
IL-6 (ng ml^{-1}) ($n = 6$)	200(16)	101(13)	0·014
PGE$_2$ (ng ml^{-1}) ($n = 6$)	319(38)	3(0)	0·019

Values are mean(s.e.m.). n.s., Not significant. *Paired *t* test

PGE$_2$ 20 ng ml^{-1} reduced 5-bromo-2′-deoxyuridine uptake by AAA smooth muscle cell monolayers by 44 per cent ($n = 4$, $P = 0{\cdot}01$).
Conclusion Very high amounts of PGE$_2$, sufficient to depress smooth muscle proliferation, are synthesized in aneurysm wall. Inhibition of cyclo-oxygenase 2 with indomethacin reduces both PGE$_2$ and IL-6 secretion. Inhibitors of cyclo-oxygenase 2 may be effective in limiting aneurysm growth rates.

Increased extracellular matrix gene expression in patients immunosuppressed with cyclosporin compared with tacrolimus

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Background The histopathology of chronic rejection is dominated by an excessive deposition of extracellular matrix proteins. This study compared expression of the genes controlling matrix deposition in renal transplant recipients immunosuppressed with either cyclosporin or the new immunosuppressive agent, tacrolimus (FK506).
Methods Renal transplant recipients were randomly allocated to receive either neoral (cyclosporin) 15 mg kg^{-1} day^{-1} ($n = 21$) or tacrolimus 0·2 mg kg^{-1} day^{-1} ($n = 21$). Tissue core transplant biopsies were performed 1 week, and 3, 6 and 12 months after transplantation. Total messenger RNA (mRNA) was extracted from glomeruli using oligo dT dynabeads and gene expression was studied by reverse transcriptase–polymerase chain reaction with quantitation of complementary DNA species using an enzyme-linked immunosorbent assay. Some 180 biopsies were analysed for the mRNA of transforming growth factor (TGF) β, collagen type III, collagen IV (alpha 2 chain), tenascin, matrix metalloproteinases and tissue inhibitor of matrix metalloproteinases (TIMP)-1 and 2.
Results TGF-β expression correlated with collagen III ($r = 0{\cdot}68$, $P = < 0{\cdot}01$), collagen IV alpha 2 ($r = 0{\cdot}35$, $P < 0{\cdot}01$), tenascin ($r = 0{\cdot}73$, $P < 0{\cdot}01$), TIMP-1 ($r = 0{\cdot}61$, $P < P0{\cdot}01$) and TIMP-2 ($r = 0{\cdot}57$, $P < 0{\cdot}01$) suggesting that TFG-β is a fibrogenic influence in human renal transplants. There were no differences in the levels of mRNA for TGF-β between recipients treated with cyclosporin and those treated with tacrolimus. Levels of mRNA for collagen III, TIMP-1, TIMP-2 and tenascin were consistently higher in patients immunosuppressed with cyclosporin ($P < 0{\cdot}01$).
Conclusion TGF-β would appear to exert a profibrotic influence in human renal transplants. The finding that tacrolimus is associated with decreased expression of a number of genes controlling fibrosis suggests that this drug may be useful in preventing chronic rejection.

Effects of Prograf (tacrolimus FK506) and Neoral (cyclosporin) on plasma total transforming growth factor β1 levels in renal transplant recipients

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Background While transforming growth factor (TGF) β1 is a powerful immunosuppressive cytokine, overexpression of TGF-β1 leads to fibrosis. The aim of the study was to compare the effects of Neoral and Prograf on plasma total TGF-β1 in renal allograft recipients.
Methods In a cross-sectional study, 27 patients had total plasma TGF-β1 measured using a commercially available enzyme-linked immunosorbent assay at the time of 6-month follow up. Patients were divided according to serum creatinine level (greater or less than 150 µmol l^{-1}) and immunosuppression (Prograf *versus* Neoral) (*Table 1*). A comparison was made between TGF-β1 levels and graft function including prevalence of rejection episodes (*Table 2*).

Results

Table 1

	Creatinine $<150\ \mu$mol l^{-1}		Creatinine $>150\ \mu$mol l^{-1}	
	Prograf ($n=14$)	Neoral ($n=4$)	Prograf ($n=3$)	Neoral ($n=6$)
TGF-β1 (pg ml^{-1})	10 508(3888)	11 212(1048)	6640(1994)*	15 865(3650)*

Values are mean(s.d.). *$P<0{\cdot}05$ *versus* creatinine $<150\ \mu$mol l^{-1}

Table 2

	TGF-β1 $<10\,000$ pg ml^{-1}		TGF-β1 $>10\,000$ pg ml^{-1}	
	Prograf ($n=10$)	Neoral ($n=2$)	Prograf ($n=7$)	Neoral ($n=8$)
Creatinine (μmol l^{-1})*	146(38)	197(75)	122(14)	149(24)
Rejection	5	1	2	3

Values are mean(s.d.)

Conclusion Patients receiving Neoral had either normal or raised levels of TGF-β1 while those in the Prograf group showed either normal or reduced levels of TGF-β1. The best renal function in both groups was observed in patients with TGF-β1 levels close to those seen in a normal population (10 000 pg ml^{-1}). Impaired graft function was associated with abnormal production of TGF-β1: reduced in the Prograf group but raised in patients receiving Neoral. In addition, a level of total TGF-β1 of less than 10 000 pg ml^{-1} was associated with a higher incidence of acute rejection and poorer graft function at 6 months.

Prediction of chronic renal transplant rejection and long-term renal function by the area under the serum creatinine *versus* time curve

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Background Chronic allograft rejection has become one of the most important challenges in renal transplantation. Early prediction of its development would greatly facilitate research into a number of the logical therapeutic interventions which are becoming available.

Methods The area under the serum creatinine–time curve (AUC) over the first 30 days following transplantation was calculated using the Excel spreadsheet for 341 consecutive renal allografts. Needle-core biopsies were performed at 3 and 6 months after transplantation and annually thereafter, and glomerular filtration rate (GFR) was measured using a single-shot isotope technique at the same time points. Chronic rejection was defined by biopsy evidence of neointimal hyperplasia, interstitial fibrosis and glomerulosclerosis with or without sustained allograft dysfunction.

Results Of 341 transplants, 1-year follow-up data were not available in 73 (33 failed, 16 died, one transferred to another centre and 23 shorter follow-up times). Eighty-eight (33 per cent) of the remaining 268 transplants demonstrated biopsy evidence of chronic rejection. This group had a significantly higher AUC than the group without biopsy evidence of chronic rejection (mean(s.e.m.) 11 500(780) *versus* 7900(430); $P<0{\cdot}001$). Forty-eight renal transplants (18 per cent) had biopsy evidence of chronic rejection associated with sustained allograft dysfunction as measured by the reciprocal of creatinine plotted against time. The AUC was higher in this group of 48 patients, compared with that for the group of 220 patients without evidence of renal dysfunction (10 000(900 *versus* 8900(440); $P=0{\cdot}07$). Furthermore, there were negative correlations between AUC and GFR at 1 month ($r=-0{\cdot}31$, $P=0{\cdot}035$), 6 months ($r=-0{\cdot}27$, $P=0{\cdot}05$), 12 months ($r=-0{\cdot}33$, $P=0{\cdot}016$) and 24 months ($r=-0{\cdot}34$, $P=0{\cdot}017$).

Conclusion The AUC calculated in the first 30 days correlates with long-term renal function and development of biopsy-proven chronic rejection.

Pre-conditioning of donor livers with prostaglandin I_2 at retrieval decreases reperfusion injury

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Background Prostaglandins have been shown to protect against a variety of liver insults including ischaemia–reperfusion injury. Decreased graft injury and improved survival have been demonstrated in animal studies of liver transplantation following donor pretreatment with prostaglandin before organ retrieval. This potential clinical application has not been examined in human liver transplantation.

Methods One hundred and six liver donors were randomly assigned to receive either prostaglandin I_2 (epoprostenol, 500 μg intravenous bolus) immediately before cold perfusion, or no drug as control. Preoperative donor and recipient characteristics were recorded. The quality of graft reperfusion at implantation was assessed visually and liver function tests were undertaken after transplantation to assess the effect of epoprostenol on graft reperfusion.

Results Donor pretreatment with epoprostenol significantly improved the rapidity and homogeneity of graft reperfusion. Epoprostenol pretreatment also significantly reduced peak values of transaminases following transplantation (SGPT: control, mean(s.d.) 851(121) units l^{-1} *versus* epoprostenol, 463(78) units l^{-1} ($P<0{\cdot}01$; *t* test); SGOT: 870(127) *versus* 463(78) units l^{-1} ($P<0{\cdot}01$); LDH: 458(95) *versus* 170(30) units l^{-1} ($P<0{\cdot}01$)). Serum levels of bilirubin and alkaline phosphatase were not significantly altered by donor pretreatment with epoprostenol.

Conclusion Liver donor pretreatment with epoprostenol improves graft reperfusion and reduces the hepatocellular injury associated with transplantation. This may have important applications in liver transplantation. Further studies are required to establish the mechanism of this effect and to define its precise role in clinical practice.

Pathophysiology of insulin, intact proinsulin and 32/33 split proinsulin after human islet autotransplantation

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Background Simultaneous islet autotransplantation (AT) and total pancreatectomy for chronic pancreatitis (CP) can prevent insulin dependence, although a proportion of patients still require exogenous insulin. In an attempt to explain insulin dependence a prospective analysis of the secretion of insulin, intact proinsulin (IPI), 32/33 split proinsulin (SPI), as well as C-peptide, was performed.

	C-peptide (mmol l^{-1})*	Glucose (mmol l^{-1}) 0 min*	Glucose (mmol l^{-1}) 2 h	Insulin (pmol l^{-1}) 30 min	IPI (pmol l^{-1})*	SPI (pmol l^{-1})*
Controls	663	3·5–5·5	<7·8	304·0	3·8	6·3
NIDDM	590	>7·8	>11·1	136·3	10·6	8·1
CP (normal GTT) ($n = 15$)	663	4·3	4·5	387·0	4·2	6·7
CP (impaired GTT) ($n = 6$)	467	7·1	10·7	101·3	3·5	4·2
Islet AT ($n = 11$)	444	7·9	17·5	144·3	9·9	30·9

Values are mean. *Fasting samples

Methods Overall 11 consecutive patients having islet AT were assessed. These were compared with patients who had CP with either impaired glucose tolerance ($n = 6$) or normal glucose tolerance ($n = 15$). In addition patients with non-insulin-dependent diabetes mellitus (NIDDM) and non-diabetic patients (controls) without CP were also evaluated. All patients received an oral (75 g) glucose tolerance test (GTT).

Results See *Table*.

Conclusion These results demonstrate insulin deficiency, raised intact and very high 32/33 SPI levels in the presence of hyperglycaemia despite C-peptide levels within the normal range in islet AT recipients. Together these results suggest that insulin processing within transplanted islet cells may be pathological.

Endothelium-derived vasoactive mediators in chronic ureteric obstruction

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Background Following complete ureteric obstruction there is a profound immunological and haemodynamic response. Recent interest has focused on the vascular endothelium to elucidate the mechanisms involved.

Methods Male Sprague–Dawley rats (400–500 g) were divided into six groups ($n = 6$ per group): (1) control; (2) control + the nitric oxide synthase inhibitor L-NMMA; (3) control + the endothelin inhibitor RO 47-0203; (4) 24 h of ureteric obstruction; (5) 24 h of ureteric obstruction + L-NMMA; and (6) 24 h of ureteric obstruction + RO 47-0203. Regional renal blood flow was assessed using quantitative autoradiography. Autoradiographs were produced from frozen kidney sections. Absolute blood flow was calculated using Kety's theory of diffusion of an inert tracer.

Results

	Cortex	Medulla
Control	806(63)	373(38)
Control + L-NMMA	581(16)	218(16)
Control + RO 47-0203	826(59)	297(12)
Ureteric obstruction	493(13)	190(10)
Ureteric obstruction + L-NMMA	412(6)	23(6)
Ureteric obstruction + RO 47-0203	687(15)	252(8)

Values are mean(s.d) blood flow (ml/s)

Conclusion Nitric oxide contributes to basal renal vascular tone. Inhibition of endothelin, however, has no effect on control blood flow. During prolonged ureteric obstruction a vasoconstricting response develops. Inhibition of nitric oxide with L-NMMA causes a further decrease in blood flow, whereas endothelin inhibition reduces the degree of vasoconstriction in the cortex. It is apparent that the renal vascular bed is responsive to the action of endothelium-derived vasoactive mediators in chronic ureteric obstruction and it is likely that they can play a protective role in the obstructed kidney.

Assessment of bone turnover with newer biochemical markers before and after parathyroidectomy

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Background The aim of this study was to determine the clinical benefit of newer bone markers in comparison to conventional bone markers in assessing bone turnover following parathyroidectomy.

Methods In total, 23 patients with primary hyperparathyroidism were studied (six male, 17 female; mean age 62 years). The newer bone markers assessed were osteocalcin, procollagen type 1 C-terminal peptide (P1CP), bone alkaline phosphatase (BALP), carboxyterminal telopeptide of type 1 collagen (ICTP) and urinary deoxypyridinoline crosslinks (UDP) compared with the more traditional bone markers, total alkaline phosphatase (AP) and urinary hydroxyproline. Samples were assessed at 2, 6, 24, 48 and 72 h after operation, and then at 6 weeks, 3, 6 and 12 months.

Results Before surgery the mean osteocalcin level was 456 ng ml^{-1} (normal range 2·7–6·9 ng ml^{-1}); this decreased after surgery to 20 ng ml^{-1} at 6 months and normalized at 1 year. Mean P1CP levels were 89 $\mu g\ l^{-1}$ (normal 38–202 $\mu g\ l^{-1}$) before surgery; the mean level then increased to a peak at 48 h (168 $\mu g\ l^{-1}$) and declined to normal at 6 weeks (116 $\mu g\ l^{-1}$). Throughout the study mean BALP levels were in the normal range (10–23 units l^{-1}) although the basal value of 20 units l^{-1} was raised at 6 weeks, stabilizing at 3 months to 15 units l^{-1}. Mean UDP levels were raised before surgery at 8·6 nmol per mmol creatinine (normal 2·0–6·0 nmol per mmol creatinine); they gradually normalized to 5·9 nmol per mmol creatinine at 6 months after operation. Mean ITCP levels demonstrated no variation with parathyroidectomy. The mean levels of both AP and urinary hydroxyproline were normal throughout although they stabilized at lower values from 3 months onwards.

Conclusion Newer bone markers are superior to conventional biochemical markers in the clinical evaluation of bone turnover following parathyroidectomy.

Potential for subfascial endoscopic perforator surgery in patients with leg ulcers

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Background Subfascial endoscopic perforator surgery (SEPS) offers potential benefit for patients with incompetent perforator veins thought to be causing ulceration. This study aimed to establish the proportion of patients with leg ulceration who might benefit from SEPS.

Methods Leg ulcers in 173 consecutive patients (227 limbs) were evaluated with ankle:brachial pressure index (ABPI) and colour duplex mapping. An ABPI of less than 0·8 was found in 29 limbs (12·8 per cent). An ABPI of less than 1·0, but greater than 0·8 was found in 25 limbs (11·0 per cent). The remaining 173 ulcers had an ABPI of more than 1.

Results Colour duplex findings for patients with an ABPI of more than 0·8 were as follows.

Distribution of incompetence	No. of limbs ($n = 198$)
Superficial only	29 (14·6)
Perforator only	6 (3·0)
Deep only	9 (4·6)
Superficial and perforator	59 (29·8)
Superficial and deep	10 (5·1)
Deep and perforator	7 (3·5)
Superficial, deep, perforator	55 (27·8)
Normal	23 (11·6)

Values in parentheses are percentages

Altogether 64·1 per cent of ulcers showed perforator incompetence (defined as perforator size 3 mm or more with incompetence demonstrated); 5·4 per cent of these patients have lateral calf perforators and 11·1 per cent of these have above-knee perforator incompetence and would therefore not be suitable for a conventional SEPS procedure. The rest have purely medial calf vein perforators. Therefore 47·6 per cent of all patients presenting with venous ulcers may benefit from SEPS. The mean number of perforators was 2·9 per patient.
Conclusion This study shows that almost 50 per cent of patients with venous ulcers have the potential to benefit from SEPS.

Health-related quality of life in patients with venous ulcers

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Background Venous ulcers affect 1 per cent of the population. Although the condition attracts relatively little attention, it has a large impact on affected patients. To quantify this impact and also to measure the effectiveness of new treatments, quality of life must be measured. Currently there is no available measure of quality of life that is specific to patients with venous ulcers. The aims of this study were to compare quality of life of patients with venous ulcers with that of the normal population, and to design a valid and reliable specific assessment of quality of life in patients with venous ulcers.
Methods Items for the initial questionnaire were selected by patient interview, literature review and expert opinion. This questionnaire and the SF-36 general health measure were given to a prospective consecutive cohort of 52 patients with clinically obvious and/or duplex-proven venous ulcers. There were 34 women (65 per cent) and the median age was 76 years. The questionnaire was assessed for reliability and validity.
Results The patients with venous ulcers had a reduced quality of life compared with age- and sex-matched UK norms. This was significant in seven of eight domains in women and six of eight domains in men ($P < 0·05$). There was no significant difference between men and women in the study population. The ulcer-specific questionnaire showed good reliability as assessed by Cronbach's α ($\alpha = 0·9$; more than 0·7 is considered reliable) and test-retest analysis ($P > 0·3$). Factor analysis identified five important health factors: social function, cosmesis, pain and dysfunction, domestic activities and emotional status. Validity was demonstrated by a high correlation with all eight domains of the SF-36 general health measure ($r > 0·58, P < 0·0001$).
Conclusion Patients with venous ulcers have significantly worse quality of life than the general population. A clinically derived specific assessment of quality of life in patients with venous ulcers has been shown to be valid and reliable.

Thrombelastography: an effective screening test for prothrombotic states

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Background A proportion of the population have an inherited thrombotic tendency predisposing to fatal thromboembolic disorders. Their investigation is expensive and often only undertaken in specialist centres. Thrombelastography (TEG) is a method of global haemostasis testing. It is a cheap, easy test to perform. Over 15–30 min a characteristic tracing is developed from measuring the strength of the clot as it forms.
Methods Some 103 consecutive patients who were attending for investigation of a suspected prothrombotic state were analysed by TEG in addition to standard thrombotic screening tests. TEG results were analysed blindly and stratified into normal, hypercoagulable, hypercoagulable or borderline. Comparison was made of the interpretation of the two sets of results (TEG *versus* thrombotic screening tests).
Results

	TEG results			
Blood test results	Normal	Hypo-coagulable	Hyper-coagulable	Border-line
Normal	31	3	10	8
Abnormal	0	4	15	16
Anticoagulants	0	16	0	0

All patients normal on TEG were found to be normal on thrombotic screening. Twenty of 23 identified as hypercoagulable had an identifiable cause, and were either receiving warfarin therapy or had a factor XII deficiency. Thirty-one of 49 patients identified as borderline or hypercoagulable had a defined prothrombotic abnormality. Eighteen patients were shown to be hypercoagulable or borderline by TEG but no prothrombotic abnormality was found.
Conclusion TEG is a simple and rapid test to perform. Patients identified as hypercoagulable or borderline merit formal investigation for an underlying prothrombotic abnormality. A normal TEG result obviates the need for formal investigation in approximately one-third of patients.

Simplired: reducing the cost of deep venous thrombosis

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Background Deep venous thrombosis (DVT) occurs commonly but clinical diagnosis is difficult, resulting in an ever increasing demand for duplex scanning, which mostly fails to reveal any abnormality. A simple reliable screening test for DVT that would reduce the demand for duplex scanning could result in considerable cost savings. Raised levels of D-dimer, a by-product of fibrin cross-linking, may be a useful serological marker for active thrombus formation. The aim of this study was to evaluate Simplired (Agen Biochemical, Brisbane, Australia), a haemagglutination assay for D-dimer requiring a simple finger prick blood sample at the bedside.
Methods Forty consecutive inpatients with suspected DVT referred for a duplex scan to assess the deep venous system formed the study population. The incidence of DVT was determined by duplex scanning (Acuson 128, Mountain View, California, USA), 11 patients had DVT and 29 had a normal deep venous system.

Results

Simplired	Deep venous thrombosis (duplex) Positive	Negative
Positive	9	7
Negative	2	22
Total	11	29

The sensitivity of Simplired in detecting the thrombus in this patient population was 82 per cent and the negative predictive value was 92 per cent. The two patients with false-negative tests had long-standing (low-risk) thrombosis. These data demonstrate, even in an unselected inpatient population, that Simplired can reliably exclude the presence of DVT likely to cause pulmonary embolism. The use of Simplired to screen requests for duplex scanning could save almost £20 000 per year in this institution.

Conclusion While awaiting prospective data to support this policy, it is concluded that Simplired may prove to be clinically useful in indicating patients with suspected DVT in whom anticoagulation may be withheld while awaiting definitive diagnosis.

Dopexamine increases conduit–coronary blood flow following coronary artery bypass grafting

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Background Although effects of vasodilators on the mammary artery *in vitro* and *in vivo* are known, there is scanty evidence for effects on flow through bypass conduits following anastomosis to the coronary circulation. Dopexamine hydrochloride, an agonist at dopamine DA$_1$ receptors and β_2-adrenergic receptors, may exert beneficial haemodynamic effects after coronary artery bypass grafting (CABG) without increasing myocardial oxygen consumption. It was hypothesized that dopexamine would increase conduit–coronary blood flow after bypass, when the coronary bed run-off will influence the flow rates at a given pressure.

Methods Human cardiac, aortic, conduit and coronary artery tissue was probed for dopamine receptors with immunohistochemical and *in situ* hybridization techniques. Patients were randomized to receive dopexamine (1 μg kg^{-1} min^{-1}) or control (saline). Following anastomosis and bypass, flow measurements were acquired from the grafts before infusion and at 15 min after infusion with ultrasound flow probes (Linton Instruments). Exclusion criteria included emergency procedures and use of other inotropes. Results are presented as mean(s.e.m.) of the absolute change for each variable and were assessed by analysis of variance. The study was approved by the University Hospitals' Ethics Committee.

Results DA$_1$ receptors were localized to the tunica media of human coronary arteries, internal mammary arteries and saphenous veins ($n = 4$). Mean age in the flow groups was 68 (range 58–74) years. A total of 25 patients were studied; 13 received dopexamine and 12 served as controls. There was no significant change in heart rate (control, 0·6(0·4) beats per min; dopexamine, 1·3(0·9) beats per min), mean arterial pressure (2·4(0·8) *versus* 0·5(1·0) mmHg) or cardiac index (0·2(0·1) *versus* 0·6(0·4)) in either patient group (all $P > 0·3$). No significant change in either mammary artery (5·6(2·3) ml min^{-1}) or saphenous vein (5·0(1·3) ml min^{-1}) graft blood flow in the control group was observed (both $P > 0·3$). However, dopexamine significantly increased blood flow in both the mammary artery (17·8(3·4) ml min^{-1}) and saphenous vein (13·5(3·3) ml min^{-1}) grafts in the experimental population (both $P < 0·05$).

Conclusion This study demonstrates that DA$_1$ receptors exist in the wall of all the vessels and grafts involved in CABG. The partially selective DA$_1$ agonist dopexamine maximizes conduit–coronary perfusion following anastomosis in patients who have undergone CABG without adversely influencing other cardiovascular parameters. This may prove beneficial in unstable patients requiring high-dose inotropic support in the perioperative period.

Duplex ultrasonography *versus* angiography in the assessment of internal carotid artery disease

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Background The degree of agreement between digital subtraction angiography and duplex ultrasonography in the assessment of internal carotid artery stenosis and occlusion was determined by retrospective analysis of duplex and angiogram reports.

Methods All patients with interpretable reports undergoing both duplex ultrasonography and angiography for symptomatic carotid disease were included.

Results Seven investigations were excluded from analysis because of technical difficulties or unclear reports. Forty-eight men and 25 women with a mean age of 65 (range 43–87) years had reports that could be used for analysis. In the symptomatic internal carotid artery there was an 85 per cent agreement rate (62 of 73 reports) between duplex scanning and angiography (kappa = 0·63 (95 per cent confidence interval 0·42–0·83)). In the contralateral internal carotid artery there was an 87 per cent agreement rate (58 of 67 reports) (kappa = 0·77(0·63–0·91)). The use of duplex reports in isolation to make a decision on suitability for surgery would have resulted in 15 per cent of patients (11 of 73) being managed inappropriately.

Conclusion Despite a superficially high agreement rate many patients would have been managed inappropriately if duplex ultrasonography alone was relied upon. Duplex scanning should not be used in isolation to assess the internal carotid artery before surgery.

Downregulation of tissue inhibitors of metalloproteinases in hepatic tissue surrounding colorectal carcinoma metastases

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Background Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) are a group of enzymes involved in extracellular matrix breakdown and remodelling. In normal tissue turnover there is a balance in activity between MMPs and TIMPs, but this balance is thought to be disrupted in favour of breakdown to facilitate invasion and metastatic spread in colorectal carcinoma (CRC). The expression pattern of TIMP-1 and TIMP-2 messenger RNA (mRNA) was examined in hepatic tissue and CRC metastases.

Methods Fresh tissue obtained from ten patients undergoing hepatic resection for metastases from CRC was immediately snap frozen in liquid nitrogen. Total cellular RNA was extracted from the metastasis, the immediately adjacent liver (within 1 cm of the metastasis) and distal liver (more than 5 cm distant), and subjected to reverse transcription (RT) using an oligo dT primer. RT–polymerase chain reaction (PCR) was performed using specific oligonucleotide primers to detect TIMP-1, TIMP-2 and β-actin (a ubiquitously expressed gene). The PCR products were analysed by non-denaturing polyacrylamide gel electrophoresis and visualized by ethidium bromide staining under ultraviolet transillumination. The specificity of the PCR products was confirmed by sequencing.

Results In all ten patients the liver metastases and distal liver expressed both TIMP-1 and TIMP-2 mRNA at equivalent levels. However in seven of the ten patients TIMP-1 expression was lower in the liver tissue immediately adjacent to the metastasis, and in nine of the ten patients TIMP-2 expression was lower.
Conclusion These results suggest that there is downregulation of both TIMP-1 and TIMP-2 in liver tissue adjacent to hepatic metastases, and that this facilitates local growth of hepatic metastatic disease.

Therapeutic effect of the matrix metalloproteinase (MMP) inhibitor, marimastat, in a gastric cancer xenograft model: relationship to MMP messenger RNA levels

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Background The matrix metalloproteinases (MMPs) are a family of proteolytic enzymes implicated in the process of tumour growth and metastasis. Marimastat is a synthetic MMP inhibitor which binds to the active site of the MMP molecule rendering it inactive.

The effect of marimastat on the growth and MMP expression of human gastric xenografts, MKN45G and ST-16, was evaluated and any observed effect was related to a change in MMP messenger RNA (mRNA) level.
Methods MKN45G and ST-16 tissue was implanted subcutaneously into 12 nude mice. Marimastat (50 mg kg^{-1} administered via osmotic minipumps) was administered daily. Animals were killed on day 28. All animal experimentation was performed according to UK Co-ordinating Committee for Cancer Research guidelines. Xenograft tissue was taken after death; mRNA was extracted, reverse transcribed to complementary DNA and complementary polymerase chain reaction (PCR) was performed. Results were normalized to GAPDH.
Results Mean tumour mass was recorded (MKN45G: control *versus* treatment 0·13 *versus* 0·20 g, P not significant; ST16: 0·15 *versus* 0·01 g, $P < 0{\cdot}05$). ST-16 tumours were not detectable macroscopically after marimastat therapy. Reverse transcriptase (RT)–PCR demonstrated mRNAs for MMP-2, MMP-7 and MMP-9, tissue inhibitors of MMPs (TIMPs) 1 and 2 and MT-MMP-1 in all xenograft control samples. MKN45G showed a significant reduction in mRNA for MT-MMP-1 after treatment ($P < 0{\cdot}05$, Mann–Whitney U test).
Conclusion Marimastat has caused ST-16 xenografts to become macroscopically undetectable. Analysis of mRNA suggests that, in addition to blocking the active site of the MMP molecule, marimastat may exert an indirect effect at the mRNA level. A significant downregulation in MT-MMP-1 mRNA was noted. This enzyme is a potent activator of MMP-2 and as such may play a pivotal role in the postulated activation cascade of MMPs.

Activated mesothelial cells produce two vascular endothelial growth factor variants: implications for tumour metastasis

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Background Vascular endothelial growth factor (VEGF) plays a central role in the development of gastrointestinal malignancies. Recently, novel receptors have been identified on tumour cells which bind VEGF$_{165}$ via its heparin-binding domain, stimulating tumour cell adhesion and motility. The production of VEGF$_{165}$ by the postoperative peritoneum may stimulate local recurrence following abdominal surgery.

The production of VEGF species by human mesothelial cells activated with the postoperative cytokines interleukin (IL) 1β and tumour necrosis factor (TNF) α was investigated.
Methods Primary mesothelial cultures were established from samples of greater omentum (ethics committee approval) and characterized by immunocytochemistry. Confluent cultures were activated with physiological doses of either IL-1β or TNF-α and analysed by semiquantitative reverse transcription–polymerase chain reaction (RT–PCR) using glyceraldehyde-3-phosphate dehydrogenase as the house-keeper gene and primers designed to detect total VEGF messenger RNA (mRNA) and its splice variants.
Results RT–PCR showed the expression of two VEGF mRNA species in activated mesothelial cells, confirmed as VEGF$_{121}$ and VEGF$_{165}$ by direct sequencing. Both variants were upregulated in a dose- and time-dependent manner.

VEGF variant	IL-1β 1 ng ml^{-1} ($n = 8$)			TNF-α 1 ng m l^{-1} ($n = 8$)		
	Total	121	165	Total	121	165
Mesothelial expression	100 (60–130)	20 (20–40)	40 (30–70)	70 (20–120)	30 (10–40)	20 (10–49)

Values are median (interquartile range) percentage increase compared with controls. All results significant at $P < 0{\cdot}05$ (Mann–Whitney U test)

Conclusion Activated mesothelial cells produce two VEGF variants, soluble VEGF$_{121}$ and heparin-binding VEGF$_{165}$. In addition to promoting angiogenesis, VEGF$_{165}$ may have a direct effect on disseminated tumour cells, promoting local tumour recurrence.

Human adenocarcinoma cells express protease-activated receptor 1 and 3 which mediate the action of thrombin

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Background Thrombin, a key enzyme in blood coagulation, has other pleiotrophic effects mediated through specific protease-activated receptor (PAR) 1 and 3. It is unclear whether both receptors are expressed in human adenocarcinomas which may be thrombin responsive.
Methods Reverse transcriptase–polymerase chain reaction was used to characterize PAR-1 and PAR-3 expression in 16 human adenocarcinoma cell lines (seven pancreas, four liver, three breast and two colon) and confirmed that all cell lines express both receptors. The functional consequences of PAR-1 and PAR-3 expression were assessed after stimulation of the MIA PaCa-2 human pancreatic adenocarcinoma cell line with either thrombin 0·1 unit ml^{-1} or thrombin receptor-activating peptide (TRAP) 100 mmol l^{-1}.
Results Both thrombin and TRAP enhanced thymidine incorporation by 65 per cent ($P = 0{\cdot}01$ *versus* control) and tumour cell invasion through Matrigel by 73 per cent ($P = 0{\cdot}05$ *versus* control). Preincubation of cells with α-thrombin was also associated with upregulation of the immediate early response gene *c-myc* at 6 h, sustained for 24 h. Differential display analysis also revealed the upregulation of *cyr61*, a putative proto-oncogene, in the cells treated with thrombin.

Conclusion These results suggest a receptor-mediated role for thrombin in controlling both the proliferation and invasion of tumour cells.

Allelic deletion at 8p11·2 is frequent in head and neck cancer and identifiable using fluorescent *in situ* hybridization on tumour imprints

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Background Head and neck squamous cell carcinoma (HNSCC) accounts for 20 per cent of malignancies worldwide. The molecular pathology of HNSCC is still poorly understood and in particular the relationship of molecular events to treatment response. The aesthetic and functional consequences of ablative surgery for HNSCC demand the identification of such markers to improve treatment planning. Cytogenetic breakpoints at 8p11·2 are associated with *in vitro* radioresistance of short-term culture HNSCC cell lines. The aims of this study were (1) to investigate the presence/absence of allelic imbalance at 8p11·2 using microsatellite analysis, (2) to confirm that allelic imbalance represents chromosomal deletion and (3) to validate a method of detecting such deletion using minimal tumour material such as would be required to avoid damaging small biopsies for histological evaluation.

Methods Fine deletion mapping of chromosome arm 8p was undertaken using a polymerase chain reaction (PCR)-based method with 15 microsatellite markers on 45 matched tumour/blood DNA pairs. Dual-colour interphase fluorescence *in situ* hybridization (FISH) on tumour imprints was performed using ANK-1 and D8S255-positive bacteriophage P1 clones (mapping to 8p11·2) as target probes and the chromosome 8 centromere repeat D8Z2 as a chromosome 8 enumeration probe.

Results Twenty-five of 45 cases showed loss of heterozygosity (LOH) with at least one marker. Loss at 8p11·2 occurred in 15 of 45 tumours with 1 of 11 in T_1/T_2 tumours *versus* 14 of 34 in T_3/T_4 tumours ($2P$ = 0·07, Fisher's exact test). LOH at 8p12 occurred in 11 of 45 cases and at 8p21–22 in 15 of 45 cases. Of the 45 tumours examined by PCR, satisfactory imprints were made from 17. Dual-colour FISH was performed comparing the number of control signals with the number of target signals. With both target probes, there was 100 per cent agreement between microsatellite analysis and FISH where the tumour was informative (17 of 17). In 17 cases where microsatellite analysis failed or the subjects were homozygous for ANK-1/D8S255, 11 showed a chromosomal deletion on interphase FISH.

Conclusion Allelic deletion at 8p11·2 is a frequent event in primary HNSCC. Loss of a putative tumour suppressor gene at 8p11·2 appears to be a late event in HNSCC tumorigenesis and may be associated with tumour progression. Interphase FISH is an effective and sensitive method of *in situ* deletion detection in head and neck tumours using tumour imprints. This method can now be applied to biopsies in a prospective study to evaluate whether deletion at that locus can predict radioresistance in primary head and neck carcinomas.

Fas-induced neutrophil apoptosis is mediated through mitrochondrial permeability and caspases

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Background Resolution of the acute respiratory distress syndrome and systemic inflammatory response syndrome is in part dependent on the induction of neutrophil apoptosis. Understanding the mechanism by which these cells die will lead to the development of novel therapeutic agents for the resolution of inflammatory diseases. Fas has been shown to induce apoptosis in a number of cell types including the neutrophil; however, the mechanism of Fas-induced neutrophil apoptosis is unknown. The aims of this study were to determine the effects of Fas on neutrophil mitrochondrial permeability and caspase activity.

Methods Neutrophils isolated from healthy volunteers were incubated with Fas monoclonal antibody CH-11 100 ng ml^{-1} and mClCCP (100 μmol l^{-1}; disrupts mitrochondrial permeability). Apoptosis was assessed by both Annexin V binding (6 h) and propidium iodide DNA staining (24 h). Mitrochondrial permeability was assessed (6 h) by DiOC6, detecting percentage of cells with disrupted mitrochondria. Caspase activity was assessed (6 h) by AFC fluorescent substrates.

Results See *Table*. Fas-induced neutrophil apoptosis was associated with an increase in caspase 3 and 8 activity as well as an increase in mitrochondrial permeability. mClCCP (which increased mitrochondrial permeability) increased caspase 3 activity only but still resulted in the induction of apoptosis. Caspase 1 had no role to play in Fas- or mClCCP-induced apoptosis.

Conclusion Fas-induced neutrophil apoptosis is associated with an increase in mitrochondrial permeability and caspase 3 and 8 activity. The effect of mClCCP demonstrates that mitrochondrial permeability increases caspase 3 activity. Regulating mitrochondrial permeability and caspase activity in inflammatory neutrophils may lead to the development of novel approaches for the resolution of inflammatory disorders.

Marimastat (BB-2516) specifically inhibits tumour angiogenesis on the chick chorioallantoic membrane

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Background Marimastat (BB-2516) is a low molecular weight orally available matrix metalloproteinase (MMP) inhibitor which has a collagen-mimicking hydroxamate structure. This facilitates binding of the zinc ion in the active site of the MMP. MMPs are necessary for invasion and metastasis but their ability to degrade basement membranes and intercellular matrix is also necessary for angiogenesis. Previously the authors have shown that the aggressive breast cell line MDA 231 acquires an angiogenic advantage by inducing fibroblasts to secrete active MMPs. The ability of marimastat to inhibit angiogenesis on the chick chorioallantoic membrane (CAM) induced by MDA 231 cells and the benign fibroblast cell line KB16F was assessed.

Methods Blood vessels invading a 20-μl collagen gel on the CAM were counted after 5 days. Marimastat was added to cell-

	Apoptosis (%)		Caspase (pmol per s per 10^6 cells)			Mitrochondrial permeability (%)
	Annexin	Propidium iodide	1	3	8	
Control	7(5)	31(5)	1·6(0·8)	15·1(2·3)	5·0(1·0)	8(3)
Fas	23(8)*	65(9)*	0·9(0·6)	76·5(15·5)*	18·5(2·4)*	35(13)*
mClCCP	18(2)*	52(3)*	1·8(0·3)	68·0(24·4)*	4·5(2·6)	29(5)*

Values are mean(s.d.). *P < 0·05 *versus* control (analysis of variance)

Assay	n	Angiogenesis (%)		P
		Marim	Control	
Marim 10^{-5} mol l^{-1} *versus* cell-free control	42	80	10	< 0·0000
Marim 10^{-6} mol l^{-1} *versus* cell-free control	31	33	10	0·0299
Marim 10^{-5} mol l^{-1} + MDA *versus* MDA control	37	12	64	0·0127
Marim 10^{-6} mol l^{-1} + MDA *versus* MDA control	36	11	64	0·0297
Marim 10^{-5} mol l^{-1} + MDA + fib *versus* MDA + fib control	52	17	100	< 0·0000
Marim 10^{-6} mol l^{-1} + MDA + fib *versus* MDA + fib control	46	65	100	0·0006
Marim 10^{-7} mol l^{-1} + MDA + fib *versus* MDA + fib control	47	90	100	0·0312

Marim, marimastat; fib, fibroblast

free gels, then MDA 231 cells were used to induce angiogenesis alone and in combination with breast fibroblasts. Median angiogenesis scores were compared against marimastat-free controls using the Mann–Whitney *U* test.

Results Marimastat significantly stimulated angiogenesis on the tumour-free CAM at 10^{-5} and 10^{-6} mol l^{-1}, but it moderately inhibited the angiogenesis induced by MDA 231 cells alone at 10^{-5} and 10^{-6} mol l^{-1}. When the MDA 231 cells were combined with fibroblasts marimastat profoundly inhibited tumour angiogenesis. This was significant down to 10^{-7} mol l^{-1} (*Table*).

Conclusion Similar to another zinc-binding MMP inhibitor, captopril, marimastat stimulates normal embryological angiogenesis in this assay. However, tumour-dependent angiogenesis is inhibited, particularly when the MDA 231 cells are inducing fibroblasts to secrete active MMPs. This selectivity implies that marimastat could specifically inhibit tumour-dependent angiogenesis without interfering with growth, development and wound healing.

Interleukin 1β gene polymorphisms correlate with survival in pancreatic cancer

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Background Polymorphisms of cytokine genes have been suggested to influence the severity and outcome of a number of conditions. Proinflammatory cytokines contribute to the cachexia associated with pancreatic cancer and also stimulate the acute-phase response, which has been found to be related to such patients' shortened survival. The present study examined the effect of a polymorphism of the interleukin (IL) 1β gene on survival in pancreatic cancer.

Methods Genomic DNA was extracted from the leucocytes of 66 patients with pancreatic cancer. Using the polymerase chain reaction a 699 base-pair fragment from the IL-1β gene was amplified and the product was subjected to Taq1 endonuclease digestion to identify the diallelic polymorphism. IL-1β production by peripheral blood mononuclear cells from 22 of the patients without jaundice or infection was also examined.

Results Median survival for allele 2 homozygotes was 82 days ($n = 4$), for heterozygotes 242 days ($n = 18$) and for allelle 1 homozygotes 256 days ($n = 44$). Patients homozygous for allele 2 of the IL-1β gene had significantly shorter survival than other groups ($P = 0{\cdot}0001$). These patients also exhibited substantially higher levels of IL-1β production ($P = 0{\cdot}022$). Homozygosity for IL-1β allele 2 predicted 120-day survival with 100 per cent specificity but, because of the low prevalence of this genotype, sensitivity was only 23 per cent. There was no significant difference in survival or IL-1β production between heterozygotes and allele 1 homozygotes.

Conclusion The possession of a genotype resulting in increased IL-1β production appears to be related to shortened survival. This may be related to the role of IL-1β in inducing an acute-phase protein response and cachexia in cancer, or may be related to changes in tumour phenotype.

Neural networks improve the prediction of survival in breast cancer

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Background Traditional prognostic indices are only able to predict outcome for patients with early or advanced breast cancer but are unreliable for the majority of patients who have a 'moderate' prognosis. Neural networks are able to 'learn' the relationships in non-linear complex data sets and thus may provide a more accurate prediction of behaviour in this group. The ability of neural networks to prognosticate for patients with breast cancer was evaluated.

Methods Data for 473 patients from the standard local British Association of Surgical Oncology database were used. Neural networks were designed with input parameters corresponding to standard Nottingham Prognostic Index (NPI) parameters, 0–7 perceptrons and a yes/no output neurone. These networks were then trained to predict survival at 36, 48 and 60 months, and validated on data not previously seen by the networks. The NPI was also calculated for all patients. Data were censored where appropriate.

Results Eighty-eight per cent of patients were in the moderate/good group according to the traditional NPI analysis ($0{\cdot}2 \times \text{size} + 1 \times \text{grade} + 1 \times \text{no. of nodes}$ ($0 = 1$, $1–3 = 2$, $>3 = 3$)). Results for the neural network prediction of overall survival are summarized below:

Time period (months)	Accuracy	PPV	NPV
36	0·84(0·70–0·99)	0·84	1·00
48	0·82(0·64–0·97)	0·81	0·86
60	0·86(0·70–0·98)	0·88	0·87

Values in parentheses are 95 per cent confidence intervals. PPV, positive predictive value; NPV, negative predictive value

To detect patients in the moderate group with a poor prognosis the artificial neural network significantly altered the weights used for the NPI parameters with size being considered far less significant ($-0{\cdot}01 - 0{\cdot}016$). In addition, the relative importance of the parameters changed for each time interval predicted.

Conclusion Neural networks provide a more powerful, robust and flexible tool for the prediction of outcome in breast cancer. The greater accuracy provided by neural network analysis will facilitate the planning of adjuvant treatment and follow-up for patients with breast cancer.

Evidence for membrane-linked, tamoxifen-insensitive receptors for oestrogen effects

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Background There is growing evidence that more than one receptor type exists for oestrogen. The traditional cytoplasmic receptor mediates the effects of oestrogen via protein synthesis that takes over 1 h to complete. However, a rapidly responsive (less than 1 min) cellular effect of oestrogen has been described recently in which membrane sodium–hydrogen exchange is activated. A better understanding of this new action may offer targets for more precise manipulation of oestrogen action in breast cancer. The mechanism of action, tamoxifen sensitivity and hormone specificity of this rapid oestrogen effect was investigated.

Methods Colonic mucosa was used as a robust model for oestrogen effects at the cellular level. Mucosal crypts from freshly resected distal colon of Sprague–Dawley rats were isolated by calcium chelation, loaded with a pH-sensitive probe (BCECF) and imaged with confocal laser scanning microscopy. Fluorescent emission intensity is expressed as percentage of basal (mean(s.e.m.)) for oestradiol 1 nmol l^{-1}, where n = number of cells sampled × number of crypts × number of colons. A t test was employed for statistics. Ethics committee approval was granted.

Results Oestradiol induced a cytosolic alkalinization (increase in fluorescent intensity) in isolated crypts within 60 s, reaching a plateau within 15 min (183(15) per cent; $n = 144$, $P < 0{\cdot}001$). However, no effect of progesterone or testosterone on cellular pH was observed in separate experiments (1–1000 nmol l^{-1}; $n = 72$, $P > 0{\cdot}8$). The oestradiol action on intracellular pH was attenuated by inhibiting (1) a sodium–hydrogen exchange isoform with ethylisopropylamiloride 10 μmol l^{-1} (105(8) per cent; $n = 72$); (2) G-proteins with pertussis toxin 1 μg ml^{-1} (137(2) per cent); or (3) prostaglandin synthesis with piroxicam 10 μmol l^{-1} (124(6) per cent) ($P < 0{\cdot}01$ for all). Neither tamoxifen 10 μmol l^{-1}, nor prevention of protein synthesis (actinomycin D 1 μg ml^{-1} and cycloheximide 1 μg ml^{-1}) inhibited the oestradiol action (all $P > 0{\cdot}8$).

Conclusion Oestradiol rapidly activates sodium–hydrogen exchange via a signal that is transduced by G-proteins and prostaglandin synthesis. This effect is independent of protein synthesis or genomic influences and is specific for oestrogen. The insensitivity of this non-genomic oestrogen action to tamoxifen may explain some of the unpredictable responses to this drug in the clinical setting. These data provide evidence for membrane receptors that offer new targets for modulating oestrogen effects in breast cancer.

Endovascular photodynamic therapy reduces the response to balloon injury in a swine model

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Background Restenosis occurs after 30 per cent of coronary and peripheral angioplasties. It is known to result from a combination of neointimal hyperplasia and geometric remodelling. To test the hypothesis that photodynamic therapy (PDT) may reduce restenosis following balloon angioplasty, the response to balloon injury in a pig model was investigated. PDT involves the interaction of non-ionizing, non-thermal light with a preadministered photosensitizer to produce cytotoxic reactive intermediates.

Methods Large White/Landrace crossbred pigs were photosensitized with 5-aminolaevulinic acid (ALA) 120 mg kg^{-1} and 4–6 h later underwent an overdistension balloon injury to both iliac ($n = 20$) and coronary ($n = 11$) arteries. The timing was calculated from previous work on the arterial pharmacokinetics of ALA. Following injury, 50 J cm^{-2} of light at 635 nm wavelength was given to ten iliac and five coronary arteries; the others acted as controls. Light was administered to the injured site via a laser fibre within the deployed angioplasty balloon. Animals were killed at 28 days and the relevant arterial segments harvested after perfusion fixing *in situ*. Morphometry of harvested sections was measured using a light microscope linked to an image analysis computer. All procedures were performed under licence from the Home Office.

Results The preinjury calibre and injury score were equivalent for both treated and control vessels. Mean(s.d.) lumen and total area were 0·8(0·5) and 2·2(0·8) mm^2 in control coronaries compared with 1·4(0·6) and 2·8(0·7) mm^2 following PDT ($P \leq 0{\cdot}005$). In the iliac segment, lumen and total areas were 8·0(4·8) and 12·5(5·4) mm^2 in controls and 9·8(3·7) and 15·2(4·3) mm^2 following PDT ($P < 0{\cdot}05$). Neointimal area was 0·7(0·6) and 0·4(0·2) mm^2 in coronary control and treated vessels respectively ($P = 0{\cdot}06$), and 0·9(0·8) and 0·8(0·5) in iliac control and treated vessels ($P = 0{\cdot}26$).

Conclusion Endovascular PDT can be delivered safely to coronary and iliac arteries via a standard balloon catheter. It favourably influences both the intimal hyperplastic and remodelling response to balloon injury and hence has potential to reduce clinical restenosis.

Thermal preconditioning protects against endotoxin-induced acute lung injury

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Background Endotoxaemia induces an acute lung injury characterized by pulmonary hypertension, arterial hypoxaemia and systemic hypotension. Preconditioning describes the process in which exposure of tissues to a subcritical event, such as hyperthermia, protects them from subsequent injury through induction of heat shock proteins (HSPs). The aim of this study was to investigate the effect of thermal preconditioning on endotoxin-induced acute lung injury.

Methods Male sheep were ventilated under general anaesthetic. Vascular catheters were placed in the femoral artery for systemic pressure and arterial gas measurements, and in the femoral vein for venous gas monitoring and infusion of endotoxin and intravenous fluids. A Swan–Ganz catheter was placed in the external jugular vein for pulmonary artery pressure and cardiac output measurements. Animals were randomized into three groups: (1) control group (C) with measurements taken at baseline and half hourly up to 150 min; (2) endotoxin group (E) receiving *Escherichia coli* endotoxin 5 μg kg^{-1} intravenously after baseline measurements; and (3) heat shock group in which HSPs were induced 24 h before endotoxin administration by raising the core temperature to 41–42°C for 20 min under anaesthesia using a warming blanket.

Results

The control group showed measurements similar to baseline measurements in all groups throughout the experiment. Endotoxin induced significant lung injury characterized by an increase in pulmonary artery pressure, hypoxia and systemic hypotension (*Table*). These changes were prevented with the induction of HSP.

Conclusion Induction of HSPs may have a therapeutic role in preventing the lung injury seen in endotoxaemia or in specific predictive surgical injuries such as that seen in severe pancreatitis and interleukin 2 toxicity.

	Endotoxin			Heat shock		
Time (min)	−30	60	90	−30	60	90
Mean arterial pressure (mmHg)	106·1(2·0)	94·4(4·5)*	94·8(2·7)*	108·2(1·8)†	103·6(1·5)†	100·0(1·4)†
Mean pulmonary artery pressure (mmHg)	14·4(0·5)*	28·2(3·2)*	33·8(1·6)*	13·6(0·5)†	16·2(0·7)†	15·6(0·9)†
Partial pressure of oxygen (kPa)	17·8(0·5)	14·7(1·1)*	11·9(1·5)*	17·2(0·9)	17·1(0·5)†	16·0(0·6)†
pH	7·40(0·01)	7·38(0·02)	7·28(0·03)*	7·38(0·02)	7·36(0·01)	7·40(0·01)†
Cardiac output (l min^{-1})	4·9(0·4)	7·4(0·2)*	8·0(0·6)*	4·8(0·4)	5·3(0·2)†	5·2(0·3)†

Values are mean(s.d.). *$P<0·05$ *versus* C, †$P<0·05$ *versus* E (analysis of variance)

Survivin, a novel inhibitor of apoptosis, and prognosis in colorectal carcinoma

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Background The successful identification of markers that provide prognostic data over and above that of conventional histopathological staging may modify decisions about adjuvant therapy in patients with colorectal cancer (CRC). The *survivin* gene codes for a recently described inhibitor of apoptosis. The present study examined its potential value as a prognostic marker.

Methods *Survivin* expression was determined by reverse transcriptase–polymerase chain reaction in resected CRC specimens from 140 patients whose overall survival was known from patient records and the regional cancer registry.

Results *Survivin* was expressed in 83 carcinomas (59 per cent). The frequency of expression did not differ significantly between tumours from different sites (right colon, left colon and rectum) or with different histopathological Dukes stages. In patients with stage B disease whose tumours did not express *survivin* the 5-year survival rate was 94 per cent, whereas in patients with *survivin*-positive tumours the survival rate was 48 per cent ($P = 0·01$). The estimated hazard ratio for death in patients whose tumours expressed *survivin* was 3·4 (95 per cent confidence interval 1·5–9·0; $P = 0·04$). In patients with stages A, C and 'D' disease, the respective survival rates were 91, 46 and 13 per cent, with no significant differences based on *survivin* expression.

Conclusion *Survivin* is a novel prognostic marker in patients with Dukes stage B CRC. The expression of *survivin* identifies a subgroup of patients with survival similar to that of patients with stage C cancers, who may benefit from adjuvant therapy. In contrast, patients with stage B disease whose tumours do not express *survivin* have a survival rate similar to that of patients with stage A disease and may not require additional therapy.

Effects of dietary supplementation on disease activity in patients with ulcerative colitis: a randomized controlled clinical study

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Background Although the aetiology of ulcerative colitis remains to be elucidated, there is evidence to suggest that disordered immune function may be important, in particular, increased immune reactivity of gut-associated lymphoid tissue resulting in autologous tissue damage. Current treatments for ulcerative colitis are anti-inflammatory and immunosuppressive. Recent studies have demonstrated the immunosuppressive properties of dietary n-3 essential fatty acids (EFAs) when ingested in large amounts for 3–6 months. A pilot study suggested that EFA supplementation may be beneficial in patients with distal proctitis. The aim of this study was to determine the effects of dietary supplementation with EFAs on disease activity in patients with ulcerative colitis.

Methods Patients with extensive and active ulcerative colitis ($n = 30$), receiving standard therapy, were randomized to receive either dietary supplementation with EFAs (eicosapentaenoic acid $3·2\ \text{g day}^{-1}$ and docosahexaenoic acid $2·4\ \text{g day}^{-1}$) or placebo (sunflower oil) for 6 months. Disease activity was assessed clinically (Truelove score), colonoscopically (Association of Gastroenterologists) and histologically using a standard scoring system. Patients were assessed before commencement of therapy, 3 months later and at the end of the study period (6 months).

Results See *Table*. There was also a significant improvement in the histological appearances at month 6 in patients in the EFA group ($P < 0·05$).

Conclusion Dietary supplementation with EFAs significantly reduces disease activity as assessed clinically, colonoscopically and histologically, in patients with extensive ulcerative colitis.

	Baseline		3 months		6 months	
	EFA	Control	EFA	Control	EFA	Control
Clinical disease activity	15 (12–17)	9 (8–12)	7 (5–9)	6 (6–10)	4 (1–5)	8 (5–10)†
Colonoscopic disease activity	2 (2–3)	2 (2–3)	1 (1–2)	1 (1–2)	1 (0–1)	1 (1–2)*

Values are median (interquartile range) scores. *$P<0·02$, †$P = 0·005$ *versus* EFA (Mann–Whitney *U* test)

Defective *versus* normal female anal sphincter anatomy

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Background The reported incidence of obstetric sphincter injury varies from 6·8 to 35 per cent. The lower figure is more in keeping with the referral rate to the anorectal clinic and the incidence of faecal incontinence. The aims of this study were to assess female anal sphincter anatomy and try to explain the above discrepancy.

Methods Endoanal ultrasonography and manometry were performed on nulliparous women in the antenatal clinic at 12 weeks' gestation. Concentric 0·5-cm level images were obtained 0·5–3·0 cm from the anal verge.

Results Thirty-six women were studied; none had a history of previous surgery or anorectal disease. Two men were also included for comparison. The mean age was 27·2 years. The mean sphincter length as determined by the position of the puborectalis sling was 2·8 cm. The two men and five women had a full 3-cm cylindrical sphincter. Others had a variable sphincter length and anterior 'defects' as below.

Sphincter length (cm)	No defect	Defect <90°	Defect 90–180°
3·0	5	7	14
2·5	2	1	3
2·0	0	4	0

Mean resting and squeeze pressures were lower in the proximal and middle cuts when there was a defect compared with a complete cylindrical ring.

Conclusion Accurate identification of sphincter length using the puborectalis sling has confirmed that a normal anatomical defect is present in the upper anterior external anal sphincter in a significant number of normal women. This explains previous over-reporting of obstetric sphincter injury.

Dysregulation of proliferation and apoptosis occurs in early human colorectal tumorigenesis

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Background Homoeostasis of colonic epithelium is maintained by an equilibrium between apoptosis and proliferation. Abnormalities of these processes enable neoplastic growth but occur at an unknown stage during the evolution of human colorectal cancer. Abnormalities of proliferation and apoptosis were sought in human colonic epithelium, at sequential stages of tumorigenesis.

Methods Fresh matched samples of cancer and distant normal mucosa were obtained from 41 patients with colorectal cancer. Polyps were obtained from six patients undergoing colectomy for adenomatous polyposis coli. Specimens were disaggregated to cell suspensions. In half of each sample, cell-cycle phase fraction was assessed by flow cytometry using propidium iodide labelling. Apoptosis was assessed in the remainder by fluorescein isothiocyanate 2′-deoxyuridine 5′-triphosphate labelling for DNA strand breaks. The apoptotic fraction was quantified using FACS analysis and expressed as a percentage. Dukes stage of cancers was assessed.

Results A linear relationship between proliferation and apoptosis was observed in normal mucosa ($P<0{\cdot}05$, Pearson's test of correlation), which was absent in both polyps and cancers. The proportion of cells in DNA synthesis phase (S phase) was greater in polyps (mean(s.d.) 13·8(10·9) per cent) and cancers (15·8(13·0) per cent) than in normal mucosa (10·5(6·6) per cent; $P<0{\cdot}05$, Mann–Whitney U test). The apoptotic fraction was lower in cancers (mean(s.d.) 18·1(16·9) per cent) and polyps (13·8(10·9) per cent) than in normal mucosa (28·1(18·0) per cent; $P<0{\cdot}05$, Mann–Whitney U test). Neither proliferation nor apoptosis were related to Dukes stage.

Conclusion Dysregulation of cell cycle and apoptosis occurs at an early stage of human colorectal tumorigenesis. New agents which promote apoptosis may be useful for cancer prevention and therapy.

Successful inhibition of inducible nitric oxide synthase does not improve experimental colitis

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Background Nitric oxide has been implicated in the pathogenesis of clinical and experimental inflammatory bowel disease. The effects of nitric oxide inhibition by arginine analogues in experimental colitis have been inconsistent. These nitric oxide inhibitors are not suitable therapeutic agents. The effect of selective inhibition of inducible nitric oxide synthase (iNOS) on experimental colitis was assessed.

Methods Rats were divided into non-colitic controls ($n=8$) and colitic groups ($n=12$ each) that received no treatment or were treated with L-nitroarginine methyl ester (L-NAME) or the selective iNOS inhibitor aminoguanidine (AMG). Colitis was induced in male Wistar rats under general anaesthetic by intracolonic instillation of 30 mg trinitrobenzenesulfonic acid in 0·25 ml 50 per cent ethanol. The therapeutic agents were given in the drinking water for 1 day before and 7 days after induction of colitis: L-NAME $500\ \text{mg ml}^{-1}$ and AMG 50, 500 and $2500\ \text{mg ml}^{-1}$. Endpoints assessed were colon macroscopic score (CMS) and the colonic citrulline concentration ([Cit]). [Cit] was assessed by high-pressure liquid chromatography after methanol extraction, and was used to indicate iNOS activity.

Results In all treatment groups nitric oxide synthesis was significantly inhibited compared with that in untreated rats with colitis. There was no dose–response correlation between AMG concentration and [Cit]. No treatment reduced the CMS.

	Control	Colitic	L-NAME ($500\ \text{mg ml}^{-1}$)	AMG ($50\ \text{mg ml}^{-1}$)	AMG ($500\ \text{mg ml}^{-1}$)	AMG ($2{\cdot}5\ \text{g ml}^{-1}$)
CMS	0 (0–1)	7 (4–8)	6 (6–8)	6 (3–7)	7 (6–9)	6 (6–7)
[Cit] (nmol per g dry weight protein)	1750 (1564–2021)	12 762 (6632–15 743)	3365 (2532–8072)*	7396 (2821–10 457)*	4834 (3846–5539)*	6021 (5280–6378)*

Values are median (interquartile range). $^*P<0{\cdot}05$ *versus* colitic (Kruskal–Wallis test)

Conclusion Oral iNOS inhibitors reduce nitric oxide synthesis in colitis but have no effect on its severity. Increasing doses of oral AMG did not reduce iNOS activity to control levels.

Incontinence and the ruptured anal sphincter

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Background Obstetrically damaged anal sphincter is the principal cause of faecal incontinence in women. The incidence of sphincter injury after vaginal delivery has been quoted as high as 35 per cent in primiparous women. This is inconsistent with current rates of referral for incontinence. The incidence of sphincter injury and its long-term symptomatic effects were assessed.

Methods A prospective consecutive study was performed; 105 primiparous women were recruited from the postnatal wards and were assessed by endoanal ultrasonography and anal manometry. Incontinence questionnaires were completed immediately and at 3 and 12 months after delivery. Those symptomatic at 12 months and with ruptured sphincters had a repeat examination at 12 months.

Results There were 78 normal vaginal deliveries, four forceps deliveries, five elective caesarian sections and 18 emergency caesarian sections. Nine of 105 (8·6 per cent) had sphincter defects including all four patients who had forceps deliveries. Manometric data provided confirmatory evidence of a sphincter defect. Patients with sphincter defects had a higher incidence of persistent new symptoms at 1 year.

Endoanal scan result	Persistent incontinence symptoms at 1 year
Normal ($n=96$)	6 (6)
Abnormal ($n=9$)	3 (33)

Values in parentheses are percentages. $P=0{\cdot}02$ (Fisher's exact test)

Conclusion Significant pelvic floor dysfunction can be predicted by postnatal endoanal ultrasonography.

Magnetic resonance evacuation proctography for assessment of anorectal dysfunction

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Background Disorders of defaecatory function are common. Evaluation often includes fluoroscopic evacuation proctography, which evaluates the function of only one of the three compartments of the pelvic floor and involves significant amounts of ionizing radiation. The aim was to show that open configuration magnetic resonance imaging scanners allow real-time imaging of patients in the erect position and are able to demonstrate dynamic rectal evacuation as well as performing detailed imaging of the soft tissues of the pelvic floor.

Methods Ten patients (nine women; median age 63 (range 21–83) years) were examined in a 0·5-T magnetic resonance unit. All patients had defaecatory difficulty, including feelings of incomplete evacuation, constipation, rectal prolapse and incontinence. The patients were seated on a custom-made wooden chair on a plastic bedpan with the anorectum at the isocentre of the magnet. A loop transmit/receive coil was placed under the bedpan. Gadolinium-DTPA 0·1 mmol kg^{-1} was administered intravenously to aid bladder visualization in eight patients. Dynamic T1 weighted real-time images were acquired at rest in mid-sagittal and coronal planes (FGR, acquisition time 4 s). Imaging was then performed during maximal squeeze and straining manoeuvres. Following this 200 ml rectal contrast (potato starch reconstituted with 1 per cent gadolinium-DTPA in water) was administered. As real-time imaging continued, the patients were asked to empty the rectum and signify when they felt defaecation was complete. The images were assembled into a cine loop for assessment of defaecatory dynamics.

Results All patients tolerated the procedure. The pelvic organs and soft tissues were clearly visualized and rectal contrast was excellent. The levator ani muscles were clearly visible in the coronal plane. No patient had asymmetrical contraction of these muscles. Intravenous contrast markedly improved bladder visualization. The two full-thickness rectal prolapses were clearly visualized. Intrarectal mucosal intussusception was seen in three patients. In seven patients a significant (greater than 2 cm) non-emptying rectocele was identified. Abnormal bladder neck descent was also demonstrated in seven patients (one with a history of stress incontinence, six asymptomatic). In one patient failure of relaxation of the puborectalis muscle (anismus) was demonstrated.

Conclusion This technique evaluates defaecatory function in a physiological position without exposure to ionizing radiation. It also gives information concerning the function of the whole pelvic floor. The technique demonstrated a significant abnormality in patients with defaecatory dysfunction when physical examination was negative or inconclusive. Further work is needed to compare this technique with established investigations of defaecatory function.

Abnormalities in mesenteric vascular control in inflammatory bowel disease

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Background The nervous control of human mesenteric veins in inflammatory bowel disease (IBD) was investigated to assess the response to exogenous neurotransmitters and electrical nerve stimulation.

Methods Mesenteric veins and control vessels were dissected from operative specimens. Ring segments of vessels were suspended in organ baths for isometric recording of tension. Cumulative dose–response curves were recorded for: noradrenaline (NA) (alone and in the presence of a subthreshold dose of neuropeptide Y (NPY)), NPY alone and adenosine 5′-triphosphate (ATP). Electrical nerve stimulation was used to assess the effect of selective receptor blockade using prazosin 10^{-6} mol l^{-1} (α_1), suramin 10^{-5} mol l^{-1} (P_{2x}-purinoceptor) and yohimbine 10^{-5} mol l^{-1} (α_2).

Results Exogenous NA caused dose-dependent constriction of control veins, which was potentiated by NPY. In veins from patients with IBD there was a loss of this potentiation (mean(s.d.) – log of the dose giving 50 per cent maximal contraction NA + NPY, 6·47(0·04) $n = 6$) *versus* 5·94(0·22) ($n = 9$); $P = 0·045$). In Crohn's disease there was a rightward shift of the dose–response curve to ATP (mean(s.d.) dose causing 25 per cent maximal contraction to potassium chloride 120 mmol l^{-1} ($p[A]_{25}$) control, 4·31(0·28)($n = 8$) *versus* Crohn's disease, 3·12(0·11) ($n = 7$); $P = 0·002$) but not in ulcerative colitis ($p[A]_{25}$ ulcerative colitis 4·47(0·29) ($n = 5$); P not significant). Nerve stimulation revealed a greatly enhanced response in IBD (mean(s.d.) tension 0·29(0·06) mN ($n = 7$) *versus* 1·35(0·34) mN ($n = 14$); $P = 0·0089$). The proportion of the contraction due to α_1, P_{2x} and α_2 receptors was 62, 13 and 8 per cent (control), and 16, 18 and 40 per cent (IBD) respectively. The residual responses were abolished by tetrodotoxin 10^{-6} mol l^{-1}.

Conclusion Abnormalities in purinergic receptors have been identified in chronic inflammatory conditions. These results similarly demonstrate changes in vascular smooth muscle response and the pattern of postjunctional receptors in mesenteric veins in IBD, which merit further investigation.

Combination of manometric and strength–duration data of the external anal sphincter to predict faecal incontinence

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Background The strength–duration curve of a muscle is thought to be a measure of its innervation. This study was designed to evaluate the ability of the strength–duration curve of the external anal sphincter to discriminate between controls and patients with faecal incontinence.

Methods Forty-three female patients with faecal incontinence were studied along with 45 age-matched women with no disorders of defaecation. A full lower gastrointestinal history, strength–duration curve of the external anal sphincter and anorectal manometry were recorded for all subjects, with the additional measurement of pudendal nerve terminal motor latency in the incontinent group.

Results Logistic regression was performed using resting and voluntary squeeze pressure and current strengths at 28 different pulse durations to develop a predictive equation for group membership. It was found that only the currents at 1 and 6 ms were significant predictors of group membership. When anorectal manometry data were included only the current required to elicit contraction at 1 ms was required. The following regression equation can be applied to predict continence in this population with a sensitivity of 95 per cent and specificity of 100 per cent.

$\mathrm{Logit}(P) = 4·1605 - 0·0559 \times$ squeeze pressure $- 0·1755 \times$ resting pressure $+ 0·8622 I_{1\,\mathrm{ms}}$ where $I_{1\,\mathrm{ms}}$ is current at 1 ms. A negative value indicates continence.

Conclusion These data show that the strength–duration curve, when used in conjunction with anorectal manometry, may be a powerful discriminatory tool for faecal incontinence. This technique may have a role in the investigation of patients with faecal incontinence.

Tumour angiogenesis and bone marrow micrometastases in colorectal cancer

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Background Tumour angiogenesis is related to outcome in several solid tumour types. It is believed to influence the metastatic process, in part by facilitating neoplastic cell release. The aim of this study was to assess the relative importance of this mechanism by evaluating the relationship between angiogenesis, the presence of disseminated tumour cells and distant relapse in colorectal cancer.
Methods Some 48 consecutive patients with colorectal cancer undergoing 'curative' surgery were studied. Preoperative bilateral bone marrow aspirates were labelled with anticytokeratin-18 fluorescent antibody and analysed by flow cytometry. The presence of any cytokeratin-positive cells in a sample of 10^5 counted cells was considered a positive result. In representative tumour sections, endothelial cells were immunostained with anti-CD 34 antibody and intratumour microvessel density was quantified by the defined area counting (DAC) method. High and low DAC scores were defined relative to a threshold value established as prognostically significant in a separate series of patients.
Results Eighteen patients had a high DAC, of whom only two had detectable bone marrow micrometastases compared with ten of 30 with a low DAC ($P = 0{\cdot}17$, Fisher's exact test). Nine patients developed metastatic disease (median follow-up 29 months), of whom eight had a high DAC and only one a positive bone marrow aspirate. The relationship between DAC and metastatic recurrence was highly significant ($P = 0{\cdot}002$, log rank test for Kaplan–Meier survival distributions) but bone marrow status was not predictive of metastasis ($P = 0{\cdot}38$).
Conclusion This study confirms the positive association between tumour angiogenesis and outcome in colorectal cancer. This does not appear to be linked with its propensity to disseminate cancer cells as indicated by bone marrow analysis.

Quantitative study of gelatinases in colorectal cancer

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Background Among the broad family of matrix metalloproteinases (MMPs), the gelatinases (MMP-2 and MMP-9) play an important role in the invasion of colorectal cancer. The amount of active and inactive gelatinases in colorectal cancers was quantitated.
Methods Tissue samples (5 mm^3) were obtained from freshly resected tumours and healthy mucosa. Tissues were homogenized in standard lysis buffer and protein was extracted. Total protein concentration was estimated by the Lowry method using commercially available kits and 20 μg protein was subjected to gelatin zymography; the normal mucosa acted as a control for the tumour. The zymograms were scanned with a laser densitometer and quantitated using the software Molecular Analyst. The ratio of the gelatinases between the tumour and mucosa was then correlated with Dukes stage of the tumour and presence or absence of vascular permeation.
Results Forty-seven tumours were used for this study. Dukes stage was as follows: five stage A, 21 stage B and 21 stage C. Eleven tumours showed vascular permeation, while this was absent in 36. $P < 0{\cdot}05$ was considered significant.

	Dukes stage			Vascular permeation		
	Stage	Tumour/ mucosa	*P**	Status	Tumour/ mucosa	*P*†
Pro-MMP-9	A	3·6(1·4)		Yes	4·5(0·9)	
	B	4·3(1·3)	0·98	No	4·4(2·0)	0·55
	C	4·3(1·1)				
Active MMP-9	A	1·3(1·0)		Yes	1·6(0·5)	
	B	1·6(0·5)	0·84	No	1·4(0·4)	0·38
	C	1·2(0·4)				
Pro-MMP-2	A	2·1(0·5)		Yes	1·1(0·3)	
	B	1·5(0·2)	0·31	No	1·6(0·2)	0·33
	C	1·4(0·3)				
Active MMP-2	A	0·7(0·3)		Yes	2·5(1·2)	
	B	1·6(1·0)	0·43	No	1·5(0·6)	0·39
	C	1·8(0·6)				

Values are mean(s.e.m.). *Kruskall-Wallis *H* test, †Mann–Whitney *U* test

Conclusion Quantitative gelatin zymography does not reveal any correlation between the amount of gelatinases, Dukes stage and the presence or absence of vascular permeation.

Role of insulin-like growth factor binding protein 3 in modulating paclitaxel-induced apoptosis in human breast cancer cells

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Background Cell growth is a balance between proliferation and programmed cell death (apoptosis). Human recombinant non-glycosylated insulin-like growth factor binding protein 3 (IGFBP-3) is a potent cell growth inhibitor with insulin-like growth factor (IGF)-dependent and -independent actions. Paclitaxel is a known apoptosis-inducing chemotherapeutic agent. The role of non-glycosylated IGFBP-3 in modulating the apoptosis induced by paclitaxel on human Hs 578T breast cancer cells was determined.
Methods Hs 578T cells were treated for 48 h with paclitaxel 25–500 nmol l^{-1} and apoptosis was confirmed by measuring a pre-G1 peak by cell-cycle analysis using flow cytometry. Cells were then preincubated with non-glycosylated IGFBP-3 500 ng ml^{-1} for 24 h followed by co-incubation with non-glycosylated IGFBP-3 and paclitaxel 75 nmol l^{-1} for a further 48 h. Western immunoblots of the conditioned media were used to detect endogenous production of IGFBP-3. Paired Student's *t* test was used for statistical analysis.
Results Paclitaxel caused a dose-dependent increase in apoptosis. The percentage of cells in the pre-G1 phase rose from 28 per cent at 25 nmol l^{-1} to 44 per cent at 500 nmol l^{-1}, in comparison to control cells (11 per cent). Preincubation of the cells with non-glycosylated IGFBP-3 before dosing caused accentuation of apoptosis of 68 per cent over that observed with paclitaxel alone ($P < 0{\cdot}05$). The amount of endogenous IGFBP-3, detected on the Western immunoblot, was increased 1·6-fold by paclitaxel compared with the control. When the cells had been preincubated with non-glycosylated IGFBP-3 the increase was by a factor of 3·6.
Conclusion As Hs 578T cells are non-responsive to IGFs in terms of proliferation and cell survival, these results indicate that IGFBP-3 may mediate apoptosis induced by paclitaxel. IGFBP-3 is a key regulatory molecule and agents altering its expression may be important in optimizing treatment.

In vivo administration of a suicide gene inhibits tumour progression in breast cancer

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Background Tumour cells that express the thymidine kinase (TK) gene are killed by exposure to the drug ganciclovir. The widespread application of this effect to treat cancer is restricted by the difficulty in transfecting tumour cells *in vivo* in sufficient numbers to induce a clinically significant 'bystander' effect. The effect of direct *in situ* introduction of the TK gene into murine breast cancer (4T1) using a liposome-mediated approach was examined.
Methods Balb/c mice (six per group) were inoculated subcutaneously with 1×10^5 4T1 tumour cells. On day 7, all tumours were injected with either 30 μl phosphate-buffered saline or 30 μl of a plasmid DNA: liposome solution containing either the TK gene (pMP6A/TK) or a control gene (pMP6A). At 48 h, groups of mice were given either intraperitoneal saline or ganciclovir 100 mg kg^{-1} for 7 days. Animals were examined daily and tumour volume was recorded using calipers.

	Mean volume at 21 days (mm^3)	
In vivo gene delivery	Intraperitoneal saline	Intraperitoneal ganciclovir
PBS	810	740
pMP6A	680	760
pMP6A/TK	675	140*

*$P = 0{\cdot}001$ (Kruskal–Wallis test)

Results At 21 days, there was a significant reduction in tumour growth in mice transfected with the TK gene (pMK6A/TK) and given ganciclovir compared with other control groups.
Conclusion Using liposome-mediated suicide gene delivery, clinically effective *in vivo* treatment of human breast cancer can potentially be achieved.

Plasma thrombospondin in early and advanced breast cancer

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Background Thrombospondin (TSP) has been shown to promote metastasis in animal models by increasing adhesion of cancer cells to endothelial cells. The aim of the study was to see if increased production of TSP by breast cancer is associated with metastatic spread.
Methods TSP was measured in the plasma of women with early breast cancer ($n = 53$) and advanced breast cancer ($n = 60$), women who had undergone surgery for breast cancer with no evidence of recurrent disease ($n = 49$), and normal premenopausal ($n = 35$) and postmenopausal ($n = 28$) women. Plasma levels were measured by radioimmunoassay developed in this unit.
Results No variation in plasma TSP was observed across the menstrual cycle. Plasma TSP in women with early breast cancer (median 461, interquartile range 346–844 ng ml^{-1}) was raised compared with that in women following surgery (227 (177–270) ng ml^{-1} ($P < 0{\cdot}001$, Mann–Whitney U test) and normal controls (225 (188–260) ng ml^{-1}) ($P < 0{\cdot}001$). Women with early breast cancer who had nodal metastases ($n = 22$) had higher levels of TSP (509 (411–997) ng ml^{-1}) than women who were node negative ($n = 31$) (297 (225–401) ng ml^{-1}) ($P < 0{\cdot}05$). Plasma levels of TSP in women with high-grade tumours (grades 2 and 3; $n = 36$) were raised compared with that in patients with grade 1 tumours ($P < 0{\cdot}05$). Plasma TSP levels in women with advanced breast cancer (588 (401–904) ng ml^{-1}) were higher than those in women with early breast cancer with no evidence of recurrent disease ($P < 0{\cdot}001$) and normal controls ($P < 0{\cdot}001$).
Conclusion Plasma TSP levels are a sensitive predictor of metastatic disease in breast cancer. TSP antagonists may prove therapeutically useful in preventing metastases.

Effect of hormone replacement therapy on screen-detected breast cancers

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Background Hormone replacement therapy (HRT) has been shown to increase the risk of developing breast cancer but cancers developing in patients receiving HRT are said to be of lower grade and better prognosis. The aims of this study were to determine the effect of HRT on the prognostic factors of cancers detected at the incident screening round and compare these with tumours detected at the prevalent round.
Methods Tumour grade and size, lymph node status, presence of carcinoma *in situ* and history of HRT use were collected from patients with screen-detected cancers, 253 incident and 325 prevalent.
Results HRT use was similar in prevalent (28·2 per cent) and incident (28·9 per cent) groups.

	Grade 1		Grade 2		Grade 3	
	HRT	No HRT	HRT	No HRT	HRT	No HRT
Prevalent	30 (41)	51 (20)	34 (46)	166 (66)	10 (14)	36 (14)
All incidents	23 (32)	35 (19)	45 (58)	98 (54)	7 (10)	40 (22)
In situ cancer	11 (48)	13 (37)	22 (52)	33 (34)	1 (14)	16 (40)

Values in parentheses are percentages

Women who took HRT had more grade 1 tumours ($P = 0{\cdot}001$) detected at the prevalent round. This difference was reduced by the incident round ($P = 0{\cdot}1$) but these women developed fewer grade 3 tumours ($P = 0{\cdot}02$). Women who developed grade 3 tumours in the incident screen were found to have taken HRT for less time (mean 36 (range 2–60) months) than those with grade 2 (55 (4–144) months) or grade 1 (48 (8–312) months) lesions. Carcinoma *in situ* occurred in a greater proportion of women taking HRT than those not (34 of 73 *versus* 63 of 180; $P = 0{\cdot}05$). No significant difference in nodal status was found.
Conclusion Women taking HRT are less likely to develop high-grade tumours and more likely to develop an *in situ* lesion.

Epidermal growth factor receptor and c-*erb*B2 expression in breast cancer progression

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Background Epidermal growth factor (EGF) receptor and c-*erb*B2 are being explored as therapeutic targets in breast cancer. This approach will be enhanced if it is effective in preinvasive as well as invasive disease. The authors have found that EGF receptor is downregulated and c-*erb*B2 is overexpressed in 95 per cent of invasive breast cancers, but little is known about the role of these factors in *in situ* disease.
Methods In frozen sections of invasive cancers with evidence of ductal carcinoma *in situ* (DCIS), EGF receptor ($n = 46$) and c-*erb*B2 receptor ($n = 40$) levels were assayed quantitatively using a

radiolabelled antibody method. c-*erb*B2 receptor levels were also quantified in 20 cases of pure DCIS. Numbers of receptors were determined by comparison with cell lines of known receptor density and compared in each element of the tumour.

Results EGF receptor and c-*erb*B2 expression each varied by a factor of several thousand. Levels of EGF receptor and c-*erb*B2 expression in DCIS associated with invasion were compared with levels in a larger group of invasive tumours ($n = 179$). The frequency distributions for expression of both factors were comparable in DCIS and invasive tumours (EGF receptor, $P = 0{\cdot}41$; c-*erb*B2, $P = 0{\cdot}68$; Mann–Whitney *U* test). Within each tumour, there was no significant difference in expression of EGF receptor of c-*erb*B2 in the DCIS and invasive components (EGF receptor, $P = 0{\cdot}419$; c-*erb*B2, $P = 0{\cdot}108$; Wilcoxon signed rank test). In addition, there was no significant difference between c-*erb*B2 expression in the pure DCIS group and that in DCIS associated with invasive disease ($P = 0{\cdot}16$; Mann–Whitney *U* test).

Conclusion These data suggest that alterations in type I growth factor receptors occur before progression of *in situ* disease to invasive cancer. High levels of c-*erb*B2 overexpression in both *in situ* and invasive areas suggest that the c-*erb*B2 product is a potential therapeutic target for the treatment of breast cancer at an early stage.

Vascular endothelial growth factor expression is affected by oestrogen and progesterone in breast cancer cells

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Background Vascular endothelial growth factor (VEGF) is one of the most potent angiogenic cytokines. Increased tumour VEGF has been shown to correlate with decreased relapse-free survival. The effect of the ovarian hormones on breast cancer progression and timing of surgical intervention remains controversial. The aim of this study was to determine the effect of oestrogen and progesterone on VEGF expression and cell growth using the breast cancer cell line MCF-7.

Methods MCF-7 cells were grown in triplicate under each of the following hormone conditions: oestradiol 1×10^{-9} mol l^{-1}; oestradiol 1×10^{-9} mol l^{-1} and progesterone 2×10^{-9} mol l^{-1} (equivalent to follicular levels of hormones); oestradiol 1×10^{-9} mol l^{-1} and progesterone $0{\cdot}5 \times 10^{-7}$ mol l^{-1} (luteal levels); and controls with no added hormones. Each day, the percentage increase in each of the flasks was counted using a histocytometer grid eyepiece. The experiment was repeated and supernatants were collected for VEGF estimation by quantitative enzyme-linked immunosorbent assay.

Results Oestrogen resulted in an increased cell growth over controls. The luteal hormone combination resulted in a smaller percentage increase in cells than the follicular combination. VEGF expression was as follows:

Hormone combination	VEGF (pg ml^{-1})
Controls	503·46
Oestradiol	650·06*
Follicular combination	650·03
Luteal combination	481·02†

Values are mean. *$P = 0{\cdot}05$ *versus* controls; †$P = 0{\cdot}05$ *versus* follicular (Mann–Whitney *U* test)

Conclusion The effect of hormones of the menstrual cycle on VEGF expression by breast cancer cells has been shown for the first time. Lower levels of VEGF expression with luteal levels of hormones may imply a lower metastatic potential in this phase of the cycle. This supports evidence favouring the luteal phase for surgical intervention in premenopausal women and may have therapeutic implications in breast cancer management.

Value of potential markers of angiogenesis in breast cancer

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Background Production of the potent endothelial mitogen vascular endothelial growth factor (VEGF) correlates in breast cancer cytosols with the development of angiogenesis (assessed by microvessel density (MVD)) and induces vascular cell adhesion molecule (VCAM) expression in endothelial cells. The aim of this study was to assess the value of serum VCAM and VEGF in predicting tumour angiogenesis and metastasis, as well as assessing response to therapy.

Methods Serum levels of soluble VCAM and VEGF were measured in women with early breast cancer ($n = 93$) and women with progressing advanced breast cancer ($n = 24$) using enzyme-linked immunosorbent assay (R&D Systems, Oxon, UK). Serum measurements were compared with known histological prognostic parameters and with MVD by immunostaining tumours with the CD31 antigen.

Results In early breast cancer serum levels of VCAM (mean 770 (range 263–1387) ng ml^{-1}) were higher than in both premenopausal and postmenopausal controls (483 and 478 ng ml^{-1}; $P < 0{\cdot}001$ and $P < 0{\cdot}01$ respectively, log *t* test). Levels of serum VEGF in early breast cancer (mean 299 (range 47–1321) pg ml^{-1}) were raised only when compared with levels in premenopausal (but not postmenopausal) women (104 (range 30–130) pg ml^{-1}; $P < 0{\cdot}01$). Levels of VCAM, but not VEGF, correlated with MVD ($r = 0{\cdot}66$, $P < 0{\cdot}001$). Serum levels of VCAM, but not VEGF, were raised in women with advanced breast cancer (mean 1236 (range 349–3914) ng ml^{-1}) compared with those in women with early breast cancer ($P < 0{\cdot}001$) and normal controls ($P < 0{\cdot}01$).

Conclusion Serum VCAM is a sensitive marker of angiogenesis in breast cancer which could be used to assess responses to therapy in women with advanced breast cancer and may have prognostic value in early breast cancer.

Mammographic surveillance following conservation surgery for breast cancer

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Background Following breast conservation surgery for breast cancer, patients are followed up, by regular clinical examinations and mammography, at intervals which vary according to local practice. However, the optimum timing for these intervals remains unclear. Concern has also been expressed regarding the necessity for mammography, in terms of its ability to detect recurrent malignant disease, and also considering the total radiation exposure which may accumulate with mammography over long periods of time. The aim of this study was to determine whether mammography undertaken following breast conservation surgery enables early detection of recurrent breast cancer.

Methods A total of 699 patients undergoing breast conservation surgery for breast cancer were identified from a database of prospectively recorded data. These patients had undergone surgery during the period 1990–1995 and had annual mammography performed according to local protocols. Local recurrence of disease, detected clinically and/or mammographically was recorded. The results of all mammograms were documented as being in one of three categories: disease recurrence, suspicious of disease recurrence or no suspicious features.

Results A total of 2181 mammograms were performed in the 699 patients. A total of 34 patients (4·9 per cent) have had clinical and/or mammographic evidence of local disease recurrence to date. Of these 34 patients, mammography detected the recurrence in eight and in a further four was reported as being suspicious of disease recurrence. Thus, mammography detected local recurrence of disease in only 12 of 34 cases. Only 12 (0·6 per cent) of 2181 mammograms revealed disease recurrence. No patients with a grade I tumour histologically and negative lymph nodes had local recurrence. In patients with grade II or III tumours (lymph node involvement) there were 19 patients with local recurrence. Mammography only detected five of these local recurrences.

Conclusion Mammographic surveillance will detect only 35 per cent of local recurrences. If annual mammography is undertaken only 0·6 per cent of mammograms will correctly identify local recurrence of disease. A selective screening policy should be considered.

Influence of preoperative magnetic resonance imaging on extent of surgical resection in breast cancer

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Background Breast magnetic resonance imaging (MRI) provides very accurate information about tumour size and location whereas size may be overestimated by clinical assessment. The impact of such information on the extent of surgical resection was assessed prospectively.

Methods One hundred and thirty-four patients with breast cancer diagnosed by triple assessment underwent surgery over 1 year. Of these patients, 40 underwent preoperative MRI using a T1-weighted 3D FLASH sequence. Images were not used to make a decision on type of surgery but were shown to the operating surgeon before operation to indicate the location of the lesion and its local extent. Clinical information and histological assessment were compared between patients who underwent MRI ($n = 40$) and those who did not ($n = 94$). Excision margins were considered to be involved if the closest margin measured less than 1 mm.

Results Ninety-six patients underwent wide local excision or segmental resection (72 per cent). There was no significant difference between the MRI group ($n = 29$) and no-MRI group ($n = 67$) in excision margin positivity rates (31 *versus* 29 per cent; $P = 0{\cdot}81$) or mean(s.d.) specimen weight (91(71) *versus* 95(88) g). Mastectomy was performed in 37 patients (28 per cent) and, similarly, there was no significant difference between the MRI group ($n = 11$) and no-MRI group ($n = 26$) in excision margin positivity rates (20 *versus* 37 per cent; $P = 0{\cdot}32$) or specimen weight (668(251) *versus* 660(258) g). Re-excision for histologically confirmed residual disease was performed in eight patients, three of 29 who had preoperative MRI and five of 67 who did not.

Conclusion These results suggest that MRI does not currently influence the extent of surgical excision, once a decision on the type of surgery to be performed has been taken. It is also suggested that the wider availability of breast MRI does not lead to a reduction in the size of excised specimens or increased margin positivity rates.

Differential display of altered gene transcripts in Barrett's oesophagus and oesophageal adenocarcinoma

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Background Knowledge of genetic changes in the oncogenesis of oesophageal adenocarcinoma from metaplastic/dysplastic epithelium remains elusive as many of these gene transcripts are unknown to current databases. The method of differential display reverse transcription–polymerase chain reaction (RT–PCR) generates transcription profiles or RNA 'fingerprints' for any given cell or tissue type. Such composite profiles of both novel and known genes may be compared with profiles of other disease states and differences in levels of gene expression identified. Differences in transcription profiles between normal, metaplastic and malignant oesophageal epithelium were characterized using differential display RT–PCR.

Methods Total RNA was extracted from 14 adenocarcinomas of the oesophagus, matched normal tissue and metaplastic epithelium. Low-stringency RT–PCR was performed using one of a set of 12 specific 3′-anchored and 5′-arbitrary primers. The products were resolved by polyacrylamide gel electrophoresis and profiles were compared between different tissue groups. Differentially expressed bands, either upregulated or downregulated, were extracted from the gel, purified, cloned and sequenced.

Results Two different primer combinations produced eight differentially expressed transcripts, which demonstrated altered expression in the majority of tumours:

	1	2	3	4	5	6	7	8
Tumour	↑14 of 14	↓12 of 14	↓12 of 14	↓14 of 14	↓14 of 14	↓14 of 14	↓14 of 14	↓14 of 14
Metaplasia	↑3 of 9	↓2 of 9	↓4 of 9	↓9 of 9	CE	CE	↓9 of 9	↓9 of 9

CE, constituitively expressed; ↑, upregulation; ↓, downregulation

Transcripts 1 and 3 were identical to known genes, thymidylate synthetase and tissue plasminogen activator. In contrast, transcripts 2 and 5 had no known homology and represent potentially novel genes. The remaining four differentially expressed products were homologous to human expressed sequence tags but of no assigned gene and are also novel targets.

Conclusion Differential display has identified an array of novel, unsuspected and known genes involved in the progression towards adenocarcinoma of the oesophagus, representing targets for further characterization to identify markers of 'at risk' lesions.

Short-segment Barrett's oesophagus is not due to gastro-oesophageal reflux disease

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Background Barrett's oesophagus with intestinal metaplasia is a consequence of severe gastro-oesophageal reflux disease. More recently, intestinal metaplasia at the squamocolumnar junction without endoscopic evidence of Barrett's oesophagus has been recognized and is termed short-segment Barrett's oesophagus. It is not known whether short-segment Barrett's oesophagus is similarly associated with gastro-oesophageal reflux disease. The oesophageal acid and bile exposure in short-segment Barrett's oesophagus was compared with that in patients with Barrett's oesophagus and patients with no intestinal metaplasia.

Methods Three groups of patients were studied: (1) short-segment Barrett's oesophagus ($n = 26$); (2) Barrett's oesophagus ($n = 25$); and (3) patients with neither intestinal metaplasia nor endoscopic Barrett's oesophagus ($n = 52$). Patients underwent 24-h ambulatory oesophageal pH studies and simultaneous 24-h ambulatory bile studies. Studies were performed when the patient had been off treatment for 10 days and no dietary restriction was advised. An abnormal pH study was defined as a deMeester score of greater than 15·0 and an abnormal bile study as an absorbance ratio value of above 0·14 for more than 5 per cent of the supine period.

Results

	Barrett's oesophagus	Short-segment Barrett's	No intestinal metaplasia
Abnormal pH study (%)	87	56	63
Abnormal bile study (%)	72	40	50
Median deMeester score	70	19	32
% supine bile reflux	20·2	1·1	4·9

The Barrett's oesophagus group differed significantly from the other two groups ($P<0\cdot05$; Mann–Whitney *U* test).

Conclusion The oesophageal acid and bile exposure in short-segment Barrett's oesophagus is significantly less than in Barrett's oesophagus and does not differ from that present in patients with no intestinal metaplasia at the normal squamocolumnar junction. Short-segment Barrett's oesophagus is not a consequence of gastro-oesophageal reflux disease. The term short-segment Barrett's oesophagus is a misnomer.

Mucin gene expression in ulcer-associated cell lineage

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Background The ulcer-associated cell lineage (UACL) is a novel stem cell line associated with chronic gastrointestinal ulcerative conditions and implicated in epithelial restitution. All three trefoil peptides, pS2 (trefoil factor family (TFF) 1), human spasmolytic polypeptide (TFF-2) and human intestinal trefoil factor (TFF-3), are expressed by the UACL, but the mucin expression profile is not known.

Methods Ten archival tissue specimens of small bowel Crohn's disease, with histologically identified UACL, were studied. Immunohistochemical analysis of the chromosome 11 secreted mucins, MUC2, MUC5B, MUC5AC and MUC6, was performed. Mucin gene messenger RNAs (mRNAs) were detected with *in situ* hybridization using ^{35}S-labelled 48-mer oligonucleotide probes.

Results The UACL glands apparent in all ten specimens demonstrated MUC5B, MUC5AC and MUC6 gene mRNA and mature protein expression. UACL did not, however, exhibit MUC2 gene expression (the dominant secreted mucin in small intestine).

Conclusion These results demonstrate, for the first time, the mucin gene expression pattern of the UACL. The UACL appears to have a distinct role in the protection and restitution of the mucosa and is associated with a supramucosal barrier composition that can be distinguished from that of the surrounding small bowel mucosa.

Prolonged acid suppression therapy is associated with gastric intestinal metaplasia

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Background Acid suppression therapy in the presence of *Helicobacter pylori* has been implicated in the development of chronic gastritis and glandular atrophy in the body of the stomach. The proposed mechanism is proximal colonization of the stomach by *H. pylori*. It remains unclear whether this process can also affect the gastric mucosa at the squamocolumnar junction where a high prevalence of intestinal metaplasia has been identified. The relationship between duration of acid suppression therapy and the presence of either *H. pylori* or intestinal metaplasia in the gastric mucosa at the squamocolumnar junction was investigated.

Methods Some 169 consecutive patients with dyspepsia attending for diagnostic upper gastrointestinal endoscopy were studied. Three biopsies were obtained from within 5 cm of the pylorus and three from within 2 cm of the squamocolumnar junction. Haematoxylin and eosin, alcian blue pH 2·5-periodic acid schiff and cresyl violet staining and immunohistochemistry for *H. pylori* were performed on all biopsies. Full drug histories were obtained and the duration of use of either proton pump inhibitors or H_2-receptor antagonists was noted. Comparisons were made using the Mann–Whitney *U* test for non-parametric data.

Results Eighty-one patients (48 per cent) had *H. pylori*. Fifty-eight (72 per cent) of these individuals had both proximal and distal gastric colonization while 23 (18 per cent) had only distal colonization. The median length of time on acid suppression therapy in the 58 patients with dual colonization was significantly greater than in the 23 with distal infection only (36 (range 0–324) *versus* 6 (range 0–180) months; $P<0\cdot05$). Eighty-eight (52 per cent) patients were *H. pylori* negative; 68 per cent of these had intestinal metaplasia within the stomach. The median length of time on acid suppression therapy in the *H. pylori*-negative patients with intestinal metaplasia was significantly longer than that in those without intestinal metaplasia (18 (range 0–216) *versus* 10 (0–192) months; $P<0\cdot05$).

Conclusion Prolonged acid suppression therapy is associated with proximal colonization of the stomach by *H. pylori* and is also an independent factor in the development of intestinal metaplasia.

Bone marrow micrometastases predict disease-specific death in carcinoma of the upper gastrointestinal tract

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Background Ber-EP4 is a monoclonal antibody raised against surface antigens of epithelium and can be used to detect micrometastases from both squamous and adenocarcinomas. Immunochemistry was carried out using this antibody to detect metastatic tumour cells in the bone marrow of patients with carcinoma of the oesophagus, oesophagogastric junction and stomach, and correlated with clinical outcomes.

Methods Bone marrow was obtained by bilateral posterior iliac crest aspiration from 43 patients who subsequently underwent resections that were potentially curative in the opinion of the operating surgeon. Mononuclear cells were isolated and cytocentrifuge preparations made and stained with Ber-EP4.

Results The presence of micrometastases did not appear to be related to the depth of penetration of the primary tumour but was commoner in tumours that had already metastasized to lymph nodes at the time of surgery (one of ten $T_{any}N_0$, 15 of 33 $T_{any}N_{1-2}$; $P<0\cdot05$, χ^2 test). Clinical follow-up was available on 29 patients (mean 12·3 (range 1–24) months). Disease-specific death was commoner when micrometastases were present as demonstrated by immunochemistry (seven of 14) than when they were absent (two of 15). Regression analysis confirmed a significant association between death from cancer during this follow-up period and immunocytological evidence of bone marrow spread ($P<0\cdot05$). Histopathological examination of operative specimens confirmed that 21 patients had undergone true D_0 resections. Clinical follow-up of this group demonstrated no deaths in 11 patients without micrometastases whereas four deaths occurred during follow-up in ten patients with Ber-EP4-positive cells present in bone marrow ($P<0\cdot05$, log rank test).

Conclusion These data support the prognostic value of Ber-EP4 immunochemistry in the identification of minimal residual disease following potentially curative resection of carcinoma of the upper gastrointestinal tract.

Dysplasia is uncommon in short-segment Barrett's oesophagus

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Background Several studies have demonstrated an increased risk of gastric adenocarcinoma in the presence of antral intestinal metaplasia. In the oesophagus, intestinal metaplasia is associated with Barrett's oesophagus and is similarly at risk of malignant change. Recently, several groups have identified intestinal metaplasia at the squamocolumnar junction in 18–37 per cent of patients without Barrett's oesophagus. The risk of malignant transformation in these patients with 'short-segment Barrett's oesophagus' is unknown. Rates of dysplasia in patients with Barrett's oesophagus, short-segment Barrett's oesophagus and those with intestinal metaplasia in the gastric antrum were compared.

Methods Some 396 patients with dyspepsia undergoing diagnostic endoscopy were biopsied. The biopsy protocol included three biopsies from each of the following sites: gastric antrum, corpus, the squamocolumnar junction and the squamous oesophagus 5 cm above the Z line. Further biopsies at 2-cm intervals were taken in patients with Barrett's oesophagus. Sections at three levels for each biopsy were stained with haematoxylin and eosin and alcian blue pH 2·5-periodic acid schiff to identify goblet cells diagnostic of intestinal metaplasia. Dysplasia was defined in accordance with standard pathological definitions and was only diagnosed when agreement was present between two pathologists.

Results Patients were divided into four groups: (1) Barrett's oesophagus ($n = 47$); (2) short-segment Barrett's oesophagus ($n = 113$); (3) antral intestinal metaplasia ($n = 80$); and (4) no intestinal metaplasia ($n = 203$). Dysplasia was present in a significantly greater proportion of patients in the Barrett's oesophagus group than in all other groups ($P < 0{\cdot}01$). Eight patients with Barrett's oesophagus (17 per cent), five patients with short-segment Barrett's oesophagus (4 per cent), one with antral intestinal metaplasia and one patient with no metaplasia had dysplastic epithelium. No patient with short-segment Barrett's oesophagus had high-grade dysplasia during treatment with high-dose proton pump inhibitor.

Conclusion Dysplasia is uncommon in short-segment Barrett's oesophagus. This suggests that surveillance endoscopy is unlikely to be indicated for these patients.

Lectin histochemistry distinguishes proliferating cell lineages at the oesophagogastric junction

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Background The aim of this study was to demonstrate whether phenotypic differences in proliferating cells at the squamocolumnar junction in patients with Barrett's oesophagus and adenocarcinoma of the oesophagus can be distinguished by lectin histochemistry.

Methods Controls and patients with Barrett's oesophagus and adenocarcinoma arising in Barrett's underwent endoscopy and biopsy. Serial sections (4 μm) were examined with monoclonal antibody to Ki 67 nuclear protein (MIB 1) and a panel of six biotin-labelled lectins: *Ulex europeus* (UEA1), *Triticum vulgaris* (WGA), *Arachis hypogaea* (PNA), *Bandeiraea simplicifolia* (GS-I), *Erythrina cristagalli* (ECA) and *Helix aspersa* (HAA), each with distinct carbohydrate binding specificity. The colour product of the streptavidin/biotin reaction was interpreted by two independent observers as positive or negative for lectin binding in the proliferative layer as defined by the MIB 1 staining. Comparisons were made using the χ^2 test.

Results Lectin binding (UEA1, PNA, GS-I, HAA) was significantly different in the proliferating compartment of squamous mucosa compared with that of gastric cardia, Barrett's and adenocarcinoma of the oesophagus. There was no significant difference between lectin binding in gastric cardia mucosa, Barrett's and adenocarcinoma arising in Barrett's.

	Squamous ($n = 16$)	Cardia ($n = 18$)	Barrett's ($n = 36$)	Adeno-carcinoma ($n = 10$)	P*	P†
UEA1 positive	4	13	28	6	0·003	0·52
WGA positive	10	15	29	9	0·3	0·78
PNA positive	0	12	29	7	0·0001	0·50
GS-I positive	0	15	31	7	0·0001	0·24
ECA positive	15	14	29	9	0·58	0·66
HAA positive	0	15	30	9	0·0001	0·84

*χ^2 test (all groups); †χ^2 test (cardia, Barrett's, adenocarcinoma)

Conclusion Lectin histochemistry distinguishes between proliferating cells of squamous and gastric mucosa but fails to distinguish between cells giving rise to Barrett's metaplastic mucosa and adenocarcinoma in Barrett's.

Role of *Helicobacter pylori* in carditis, metaplasia and gastro-oesophageal reflux disease

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Background The relationship between gastric carditis, intestinal metaplasia (IM) and gastro-oesophageal reflux disease was investigated, with particular reference to *Helicobacter pylori* infection.

Methods Fifty patients with heartburn underwent endoscopic biopsy as follows: squamocolumnar junction (three biopsies), gastric body (two) and gastric antrum (two). Subsequently, patients underwent stationary oesophageal manometry and 24-h pH studies. Biopsies were stained with haematoxylin and eosin/Giemsa and the presence (HP +) or absence (HP −) of *H. pylori* was determined. Inflammation in cardiac-type mucosa (carditis) was assessed using the revised Sydney classification. IM was defined by the presence of goblet cells.

Results

	No cardiac-type mucosa ($n = 11$)	Cardiac mucosa	
		HP + ($n = 11$)	HP − ($n = 28$)
LOSP (mmHg)	17·0 (7·8–25·0)	9·8 (2·4–25·0)	8·7 (5·3–13·9)
Total percentage of time at pH < 4	2·3 (1·1–7·2)	4·9 (2·2–22·2)	12·9 (4·4–19·7)*
Supine percentage of time at pH < 4	0·0 (0·0–0·6)	3·1 (0·5–29·1)	6·5 (0·1–19·0)*
IM at cardia	0 of 11	7 of 11†	7 of 28

Values are median (interquartile range). LOSP, lower oesophageal sphincter pressure. *$P < 0{\cdot}05$ *versus* no cardiac mucosa (Mann–Whitney U test); †$P < 0{\cdot}01$ *versus* no cardiac mucosa, $P < 0{\cdot}05$ *versus* HP − (Fisher's exact test)

Cardiac-type mucosa was identified in 39 patients and was inflamed in 36. Inflamed cardiac mucosa was associated with *H.*

pylori infection in 11 patients with *H. pylori* being absent in 25 patients. The presence of cardiac-type mucosa ($n = 39$) was associated with a reduced LOSP (9·0 (4·0–15·0) *versus* 17·0 (7·8–25·0) mmHg; $P = 0{\cdot}08$) and increased oesophageal acid exposure (total percentage of time at pH less than 4: 9·9 (2·9–19·7) *versus* 2·3 (1·1–7·2) per cent; $P < 0{\cdot}05$) compared with that in patients in whom cardiac-type mucosa was not present ($n = 11$). IM was present within cardiac mucosa in 14 patients (28 per cent). In 13 of these patients there was no evidence of IM at any other location within the stomach.

Conclusion When present, cardiac-type mucosa was invariably inflamed and was associated with reduced LOSP and increased oesophageal acid exposure. Carditis was associated with *H. pylori* infection in one-third of patients. Localized IM arising in inflamed cardiac mucosa may occur in the setting of either *H. pylori* infection or gastro-oesophageal reflux disease.

Comparison of expression of cell adhesion molecules in gastric cancer with soluble isoforms in serum

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Background Cell adhesion molecules (CAMs) are expressed by many cancers as well as by normal tissues. They play an important role in the growth, differentiation and dissemination of tumours. Recently, soluble isoforms of a number of these molecules have been described in the sera of patients with a variety of diseases. The aim of this prospective study was to quantify expression of the CAMs E-selectin, ICAM-1 (interstitial CAM) and VCAM-1 (vascular CAM) in the sera of patients with gastric cancer before operation and to compare the levels of these molecules with expression by the tumour. Correlations between CAM expression and known prognostic indicators were also examined and serum levels of the CAMs in patients were compared with those in healthy age- and sex-matched controls.

Methods Thirty-five patients with gastric cancer and 16 controls were studied. Serum levels of CAMs were determined by enzyme-linked immunosorbent assay. Expression on the primary tumour was determined by two-colour flow cytometry with cytokeratin gating.

Results Serum E-selectin levels were lower in patients than in controls ($P = 0{\cdot}01$) and ICAM-1 levels were higher in patients than controls ($P = 0{\cdot}03$). Serum levels of ICAM-1 were higher in patients with poorly compared with well differentiated tumours ($P = 0{\cdot}03$). Tumour ICAM-1 expression was significantly higher in lymph node-positive compared with node-negative tumours ($P = 0{\cdot}03$) and in poorly *versus* well differentiated tumours ($P = 0{\cdot}02$). VCAM-1 expression in early gastric cancers (T_1) was significantly lower than that in locally advanced (T_4) tumours ($P = 0{\cdot}01$). There was no correlation between expression of these CAMs on primary gastric cancers and levels of their soluble isoforms in sera.

Conclusion Altered expression of CAMs was demonstrated in the sera of patients with gastric cancer compared with controls and soluble ICAM-1 levels correlated with grade of tumour. Tumour expression of ICAM-1 and VCAM-1 correlates with known prognostic indicators. This is the first study to compare serum levels of CAMs with tumour expression in patients with gastric cancer, and no correlation has been demonstrated.

Development of an assay to detect soluble fms-like tyrosine kinase in the sera of patients with colorectal and breast cancer

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Background Vascular endothelial growth factor (VEGF) is one of the key angiogenic cytokines, essential for the growth and metastasis of solid tumours. It acts via two high-affinity receptors, kinase domain region (KDR) and fms-like tyrosine kinase (FLT-1). FLT-1 exists as both a membrane-fixed form and a soluble form (sFLT-1). sFLT-1 is the only known natural direct antagonist of VEGF. The aim of this study was to develop a quantitative enzyme-linked immunosorbent assay (ELISA) for sFLT-1 and to determine whether sFLT-1 is detectable in the serum of patients with colorectal and breast cancer.

Methods A ligand capture quantitative ELISA was designed using VEGF, sFLT-1, anti-sFLT-1 and anti-immunoglobulin G. Serum was collected before operation from 50 patients with colorectal cancer and 43 with breast cancer. Serum was available after operation for 17 of the patients with colorectal cancer. The serum of 20 healthy volunteers was also assayed.

Results The intra-assay and interassay coefficients of variation for the assay were 6–11 per cent and 2–14 per cent respectively ($r = 0{\cdot}98$–$0{\cdot}86$). Only one of the controls had a detectable serum level of sFLT-1. Six of the 50 patients with colorectal cancer had a detectable level of sFLT-1. Of the 17 postoperative samples assayed, three patients who had a positive preoperative sFLT-1 sample showed a significant reduction in postoperative level. None of the 14 patients with a negative sample before operation seroconverted after operation. Twenty-two of 43 patients with breast cancer had a detectable level of sFLT-1. Oestrogen receptor-positive tumours had higher levels (mean 5·56 ng ml^{-1}) than oestrogen receptor-negative tumours (2·24 ng ml^{-1}) although this was not statistically significant. Unlike serum VEGF, no correlation was found with stage of either cancer.

Conclusion A quantitative ELISA capable of detecting sFLT-1 in human serum was developed successfully. This is the first report of sFLT-1 detected in the sera of patients with cancer. The difference in detection rates between breast and colorectal cancers may reflect a biological difference between the two. The role of sFLT-1 as an antiangiogenic agent needs further study.

Frequent loss of 5q21 in head and neck cancer without inactivation of the *APC* gene implies the presence of another putative tumour suppressor gene at 5q21

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Background Head and neck squamous cell carcinoma (HNSCC) accounts for 20 per cent of malignancies worldwide. The molecular pathology of HNSCC is still poorly understood but genome-wide allelotyping by several groups has identified the long arm of chromosome 5 to be a frequently deleted region in HNSCC. 5q21 is a region frequently deleted in advanced lung cancer as well as in oesophageal and gastric cancer. 5q21 is also the chromosomal location of two well characterized tumour suppressor genes adenomatous polyposis coli (*APC*) and mutated in colon cancer (*MCC*). Over 80 per cent of known mutations of the *APC* gene occur in the mutation cluster region of exon 15 leading to truncation of the APC protein. The aims of this study were (1) to examine three polymorphic loci at 5q21 for loss of heterozygosity and (2) to examine the *APC* gene for protein truncating mutations in those which show loss of heterozygosity.

Methods Analysis of the polymorphic markers DP1, YN5.64 and MCC on a panel of 36 HNSCCs was undertaken using a polymerase chain reaction (PCR)-based method with fluorescently labelled oligonucleotides. Mutation analysis of the *APC* gene was performed using the protein truncation test. Segments 2 and 3 of exon 15 of the *APC* gene were amplified by PCR. Linked T7 transcription and translation was performed using the Promega system. The [^{35}S]methionine-labelled protein products were resolved by sodium dodecyl sulphate–polyacrylamide gel electrophoresis and visualized autoradiographically.

Results Ten of the 26 tumours informative for at least one marker showed loss of heterozygosity at one or more marker; seven of 19 at DP1, four of 18 at YN5.64 and six of 18 at MCC. No protein-truncating mutations at the mutation cluster region of the *APC* gene were identified.

Conclusion Allelic deletion at 5q21 around the *APC* locus is a frequent event in head and neck carcinogenesis. However, no truncating mutations of the *APC* gene were detected. This suggests that either the *APC* gene is inactivated by another mechanism in head and neck cancer or that another putative tumour suppressor gene involved in head and neck carcinogenesis maps to 5q21.

Transcription of angiotensin receptor in normal and diseased breast

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Background Angiotensin II is the biologically active peptide of the renin angiotensin system. Most of the known physiological actions of angiotensin II are mediated via its type I (ATI) receptor. Angiotensin II regulates growth and development of tissues and thus may be an important factor in tumour progression. Using a specific monoclonal antibody (6313/G2) the authors have previously shown ATI receptor expression in breast tissue. The aim of the study was to confirm previous results and relate the expression of ATI receptor protein and gene to disease progression.

Methods Samples were obtained from 62 patients aged 32–91 years. These were subjected to analysis by reverse transcriptase–polymerase chain reaction (RT–PCR) using specific primers designed to amplify a 210-base pair fragment of the ATI receptor complementary DNA (cDNA). These results were semiquantitated by densitometry. Formalin-fixed paraffin-embedded breast tissue sections were examined by immunocytochemistry using the 6313/G2 monoclonal antibody.

Results The ATI receptor target sequence was consistently amplified using RT–PCR in all breast samples analysed. The sample group included benign tissue ($n = 7$), normal non-diseased breast ($n = 8$), breast cancer ($n = 47$) and axillary lymph node metastases ($n = 3$). The expression by RT–PCR was variable but densitometric analysis revealed a higher level of transcription of the receptor in normal breast samples compared with breast cancer tissue ($P < 0{\cdot}01$). The difference in ATI transcription between benign and malignant breast disease was less well marked ($P < 0{\cdot}05$). Transcription of ATI receptor messenger RNA (mRNA) in metastatic axillary lymph nodes was, perhaps unexpectedly, increased. There was consistent transcription of receptor mRNA in the breast cancer cell lines MCF-7 and T47D. A similar pattern of expression of the receptor protein was observed by immunocytochemistry, with benign samples showing a higher level of expression than malignant lesions ($P < 0{\cdot}05$). Results from slot blot RNA hybridization to a specific double-stranded cDNA probe revealed stronger signals in benign samples compared with malignant samples.

Conclusion Angiotensin II may play a role in growth and development of breast cancer.

Effect of tamoxifen treatment on *MUC-1* expression in primary breast cancer

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Background Increased *MUC-1* expression reduces cell–cell adhesion and facilitates cell detachment thus increasing metastatic potential. Tamoxifen decreases the incidence of both local and metastatic breast cancer recurrence but the mechanisms of its action have not been determined fully. The effect of administering tamoxifen for 3 weeks before operation on *MUC-1* expression in primary breast tumours was established.

Methods Patients were matched for age, tumour grade and axillary status and treated with either oral tamoxifen 20 mg per day ($n = 46$) or received no medication ($n = 51$) for the 3-week interval between assessment and surgery. Specimens were snap frozen at the time of surgery and *MUC-1* expression was assessed using flow cytometry. Optimum staining methodology was determined, rendering cells fixed but permeable to the NCL-MUC-1 antibody (Novocastra). Dual-parameter labelling, with a goat-antimouse fluorescein isothiocyanate-conjugated secondary antibody to detect the NCL-MUC-1 primary antibody and propidium iodide to identify nucleated cells, was used. The percentage of cells expressing *MUC-1* was determined with respect to an isotype control. Fluorescent bead standards were used to quantify the number of equivalent soluble fluorescent molecules of *MUC-1* per cell.

Results A lower percentage of cells expressed *MUC-1* following 3 weeks of tamoxifen treatment (median 18·2 *versus* 28·5 per cent; $P = 0{\cdot}03$, Mann–Whitney *U* test) and a lower level of *MUC-1* expression per cell was seen following tamoxifen treatment (median 31 519 *versus* 39 773 molecules per cell; $P = 0{\cdot}04$, Mann–Whitney *U* test).

Conclusion *MUC-1* expression can be monitored by flow cytometry. *MUC-1* levels in patients receiving tamoxifen for 3 weeks before operation are significantly lower than those in a comparable group of patients receiving no treatment. Tamoxifen therapy in the preoperative period significantly reduces the expression of *MUC-1* in primary breast cancer, which has been implicated in the evolution of metastasis.

A significant increase in the level of the matrix metalloproteinase (MMP) 2–tissue inhibitor of MMP-2 complex in gastric cancer is unaffected by MMP inhibition

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Background The matrix metalloproteinases (MMPs) are a family of proteolytic enzymes implicated in the process of tumour growth and metastasis. Their inhibition is a new treatment. Reverse transcriptase–polymerase chain reaction (PCR) was used to quantify the MMPs and tissue inhibitors of MMPs (TIMPs) in gastric cancer and these findings were confirmed using zymography and immunohistochemistry. Changes in protein expression in patients with advanced gastric cancer treated with MMP inhibitor were also assessed.

Methods Messenger RNA (mRNA) extracted from 20 gastric cancers and normal mucosa samples was reverse transcribed to complementary DNA and competitive PCR was performed. Zymography was used to quantify the active and latent forms of MMP-2 and MMP-9. Immunohistochemistry with anti-MMP-2 and anti-MMP-9 antisera was performed on five cancer samples. Biopsies taken from 14 patients with advanced gastric cancer before and after treatment with MMP inhibitor were subjected to zymography.

Results The mRNAs for MMP-2 and MMP-9 and TIMP-2 were expressed significantly more frequently in tumour than in normal mucosa ($P = 0{\cdot}05$, χ^2 test). A significantly increased quantity of mRNA for MMP-2 and TIMP-2 was seen in gastric cancer ($P < 0{\cdot}05$, Mann–Whitney *U* test). Zymography showed significantly increased expression of MMP-2 and MMP-9 protein in tumour ($P < 0{\cdot}05$, Mann–Whitney *U* test). Immunohistochemistry confirmed these findings. After treatment with MMP inhibitor patient samples showed no difference in protein expression.

Conclusion A significantly increased level of MMP-2 and TIMP-2 mRNA in gastric cancer was observed, as well as translation into functioning MMP-2 protein. When patients with gastric cancer were given MMP inhibitor the MMP-2 protein level was unaffected. Treatment with MMP inhibitor may alter the MMP-2/TIMP-2 ratio rather than the absolute MMP-2 level. This work highlights the importance of MMP/TIMP ratios.

Clonal evolution in hepatocellular carcinoma

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Background Whether human cancers develop as monoclonal growths derived from a single malignant clone, or whether each tumour contains multiple clones of malignant cells, is an important but unresolved question that may have considerable therapeutic implications. This question has been addressed in human hepatocellular carcinomas (HCCs), using the novel but well validated technique of arbitrarily primed polymerase chain reaction (PCR) to create high-resolution fingerprints of genomic DNA.

Methods Thirty-one HCCs were sampled from eight cirrhotic livers removed at orthotopic liver transplantation. Two or more sectors of each tumour were separately microdissected from paraffin-embedded formalin-fixed sections, and DNA extraction was performed. A total of 76 samples were amplified with two different ^{33}P-labelled arbitrary primers in appropriate conditions. Polyacrylamide gel electrophoresis of the PCR product was then performed.

Results In every HCC of 6 mm or less in diameter ($n = 18$; mean diameter 4·7 mm), all sectors of the tumour had identical DNA fingerprints, indicating that these tumours do represent clusters of monoclonal cells all derived from a single precursor. By contrast, every HCC greater than 6 mm in diameter ($n = 13$; mean diameter 15·4 mm) showed distinct DNA fingerprints in each sector sampled indicating clonal divergence within each tumour ($P = 0{\cdot}0008$, t test). When synchronous HCCs were present, no tumour had the same DNA fingerprint as any other.

Conclusion These results suggest that while HCCs start off as monoclonal growths, once they exceed a certain size (more than 6 mm diameter) clonal differentiation occurs, so that larger HCCs contain several subpopulations of cells with distinct genomic characteristics. Each new subclone is likely to have different invasive and metastatic capabilities, and this genetic instability may enhance the rate of tumour progression. Current concepts of therapy in HCC may require re-evaluation based on this information on clonal evolution.

Transforming growth factor β-1 increases vascular endothelial growth factor level independent of growth inhibition

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Background Transforming growth factor (TGF) β-1 is a multifunctional cytokine that can inhibit the proliferation of both tumour cells and endothelial cells. However, many tumour cells escape this growth inhibition. TGFβ-1 has been shown to increase angiogenesis in an indirect manner. Vascular endothelial growth factor (VEGF) is the most potent of the angiogenic factors that the authors and others have shown to play a role in breast cancer.

Methods Two breast cancer cell lines, BT474 and MDA-MB-231, cell lines of primary and metastatic origin respectively, were treated with TGFβ-1. VEGF production and cellular proliferation was assessed. VEGF production was examined by enzyme-linked immunosorbent assay and standardized to total cellular protein measured by the Bradford assay. The proliferation of cell lines was examined by direct counting, propidium iodide staining and flow cytometry and by a proliferation assay utilizing the conversion of tetrazolium salt.

Results TGFβ-1 5 ng ml^{-1} significantly increased VEGF production in BT474 cells compared with control cells (mean(s.d.) 6·0(0·7) *versus* 4·1(0·7) pg per μg protein; $P = 0{\cdot}03$). TGFβ-1 increased VEGF production by MDA-MB-231 cells (21·2(2·3) *versus* 12·1(2·4) pg per μg protein at 7·5 pg per μg protein ($P = 0{\cdot}03$) and 25·2(5·5) *versus* 12·1(2·4) pg per μg protein at 10 pg per μg protein ($P = 0{\cdot}007$)). TGFβ-1 did not inhibit the growth of either cell line.

Conclusion These results suggest a role for TGFβ-1 in breast cancer angiogenesis independent of TGFβ-1-mediated growth inhibition.

Early prostate cancer is associated with changes in protein kinase C isoenzyme expression

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Background Protein kinase C (PKC) is a family of 12 isoenzymes, with a central role in regulation of cell proliferation, differentiation and apoptosis. Previous studies have suggested changes in overall PKC activity in prostatic cancers. In this study an attempt was made to identify which isoenzymes are important.

Methods Expression of PKCα, PKCβ, PKCδ, PKCε, PKCγ, PKCι, PKCλ, PKCμ, PKCθ and PKCζ and their receptor for activated C-kinase 1 (RACK-1) was determined immunohistochemically in formalin-fixed paraffin wax-embedded archival tissue specimens of early prostatic adenocarcinoma ($n = 23$), obtained at radical prostatectomy, and compared with benign prostate removed at primary cystectomy ($n = 10$), using specific monoclonal antibodies. Slides were scored by two of the investigators. Results were analysed by χ^2 test.

Results There was a decrease in PKCβ expression in cancerous compared with benign epithelium ($P < 0{\cdot}0001$). PKCβ expression was also decreased in the stroma immediately surrounding the cancer ($P < 0{\cdot}01$). PKCε expression increased ($P < 0{\cdot}0001$), and this was inversely correlated to PKCβ expression ($P < 0{\cdot}001$). PKCζ expression was increased in the cancers ($P = 0{\cdot}015$), but this did not correlate either with expression of PKCβ or PKCε, PKCα, PKCδ, PKCγ and PKCθ were not expressed in the epithelium of either the cancers or the benign prostates. PKCλ, PKCι, PKCμ and RACK-1 expression was not significantly different between the two groups.

Conclusion PKCε is known to cause proliferation and has been suggested to act as an oncogene via *Raf-1*. PKCβ has been shown to cause suppression of apoptosis in other tissues. These findings suggest that alteration in the balance of PKC isoenzymes involved in tumour development and suppression may also have a pivotal role in the development of prostate cancer and thus raise exciting new possibilities for novel treatments.

Receptor to macrophage colony-stimulating factor is upregulated in bony metastases from prostate cancer

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Background The receptor to macrophage colony-stimulating factor (MCSF) may play an important role in the invasion of tumour cells. Transfection of the activated receptor into a normally non-invasive murine cell line rendered the cell line invasive *in vitro* and able to form metastases in an animal model.

Methods To determine whether MCSF or its receptor is important in the development of bone metastases from prostate cancer, the expression of messenger RNA (mRNA) to its receptor and ligand in primary prostate cancers and bony

	MCSF		MCSF receptor		PTHrP		PTHrP receptor	
	No. positive	Median score	No. positive	Median score	No. positive	Median score	No. positive	Median score
Primary prostate cancer ($n = 21$)	14	2 (0–6)	10*	3 (0–6)	20	3 (0–9)	4	0 (0–3)
Bone metastases ($n = 13$)	10	3 (0–9)	11*	6 (3–6)	6	2 (0–6)	12	6 (0–9)

Values in parentheses are ranges. *Preliminary result; more samples to follow

metastases from prostate cancer was examined using *in situ* hybridization.

Results Preliminary results have shown that bone metastases from prostate cancer produce greater amounts of mRNA to MCSF receptor than primary prostate tumours ($P = 0{\cdot}01$; two-tailed Mann–Whitney *U* test). The receptor to parathyroid hormone-related protein (PTHrP) is increased in bony metastases from prostate cancer ($P = 0{\cdot}001$; χ^2 test). A positive correlation between PTHrP receptor and MCSF protein was found ($P = 0{\cdot}01$; two-tailed Spearman's rho).

Conclusion Activation of both receptors leads to increased production of urokinase plasminogen activator, which breaks down bony matrix creating space for tumour growth and releasing growth factors present in bone. The expression of receptors to PTHrP and MCSF enables tumour cells to survive in bone.

Combination cytokine and suicide gene therapy results in enhanced tumour regression and regression of distant metastases

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Background Suicide gene therapy results in the regression of localized tumours. *In vivo*, tumour regression is mediated by a localized antitumour immune response. The aim of this study was to determine if tumour regression could be enhanced by strategies designed to upregulate the immune response. Such an approach may also result in the generation of a systemic antitumour response.

Methods Combination cytokine and suicide gene therapy was investigated in a murine model for the treatment of colorectal carcinoma. The MC26 colon carcinoma cell line was transduced *in vitro* with genes expressing herpes simplex virus type 1 thymidine kinase (HSV1-TK), interleukin (IL) 2 and granulocyte–macrophage colony-stimulating factor (GMCSF) to generate the MC26TK, MC26IL-2 and MC26GMCSF cell lines. Cytokine gene expression was confirmed by bioassay. Subcutaneous tumours were generated in Balb\C mice by injection of combinations of a total of 1×10^6 cells of the above cell lines. All animals received a second injection of 1×10^6 cells of the unmodified MC26 cell line on the opposite flank. After 7 days, animals were treated with ganciclovir 75 mg kg^{-1} twice daily for 5 days. Tumour volume was then determined. Animals were divided into seven groups. Experiments were performed under the Animals Act 1986.

Results HSV1-TK-mediated therapy results in the regression of localized tumours (group 2). Combination therapy with HSV1-TK, IL-2 and GMCSF (group 5) results in enhanced tumour regression compared with HSV1-TK alone (group 2) ($P < 0{\cdot}05$). In addition, animals in group 5 showed regression of MC26 tumours on the opposite flank (mean tumour volume 232 mm^3) compared with controls (group 1) ($P < 0{\cdot}05$).

Conclusion Combination cytokine and suicide gene therapy results in enhanced tumour regression and the generation of a systemic antitumour response with the regression of distant metastases.

Objective assessment of the effect of sleep deprivation on surgical psychomotor skill

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Background Sleep deprivation has been shown to impair cognitive performance. The present study quantified the effect of sleep deprivation on surgical psychomotor skills.

Methods Objective criteria of psychomotor skill were measured using a computerized surgical assessment device which is undergoing validation as an assessment tool. The device tracks the movement of the surgical instruments, time-stamps and smooths the raw x,y,z data with a fourth-order Butterworth filter and calculates the average number of errors and the time taken for each exercise. Six surgeons in training (median age 31 (range 26–33) years) were studied on six separate nights, at 1-week intervals, with practice effects controlled by a Latin square design. Assessments were carried out twice in the evening and twice the following morning, after one of three conditions: an undisturbed night (control), a mock night on call and a night with no sleep. All subjects had been pretrained on the tasks and completed a standard stress and arousal questionnaire after each test.

Results

Group	1	2	3	4	5	6	7
Cell line	MC26	TK:MC26	TK:IL-2	TK:GMCSF	TK:IL-2:GMCSF	IL-2	GMCSF
Ratio (%)	100	50:50	50:50	50:50	50:25:25	100	100
Mean tumour volume (mm^3)	410	43	26	25	17	208	414
P*		$< 0{\cdot}01$	$< 0{\cdot}01$	$< 0{\cdot}01$	$< 0{\cdot}01$	$< 0{\cdot}05$	n.s.

n.s., Not significant. *Mann–Whitney *U* test

	Difference in performance (evening score – morning score)			Deterioration (%) (no sleep *versus* control)	Overall score
	Control	On call	No sleep		
Errors	–0·43(0·18)	–0·11(0·19)	+0·38(0·19)	20	3·48(0·08)
Time	–0 97(0·36)	–0·49(0·35)	+0·44(0·45)	14	10·10(0·20)

Values are mean(s.e.m.)

Repeated measures analysis of variance for a Latin square showed a significant linear trend across sleep conditions, relative to baseline, for total time (F(1,20) = 8·40, P = 0·009) and error score (F(1,20) = 8·49, P = 0·009), with a non-significant non-linear trend. Surgeons awake all night showed increased stress and decreased arousal (F(1,20) = 17·52, P < 0·001 and F(1,20) = 80·08, P < 0·001 respectively), which paralleled the decrement in operative performance. Stress and arousal correlated (r = –0·640, P < 0·001; n = 72).

Conclusion Sleep deprivation impaired psychomotor performance on simulated surgical tasks. The performance decrement remained significant after arousal was taken into account as a co-variate (P = 0·011), but not after stress was used as a co-variate (P = 0·105), suggesting that sleep deprivation mediates its effect via increased stress rather than decreased arousal.

New method for assessment of hepatic dysfunction using near-infrared spectroscopy and indocyanine green

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Background Hepatic indocyanine green (ICG) clearance is an objective method of assessing liver function. Direct measurement of ICG concentration in the hepatic tissue may provide the most accurate way to study the kinetics of ICG in the liver including its uptake and biliary excretion. Near-infrared spectroscopy (NIRS) can assess the hepatic clearance of ICG non-invasively but has not been assessed objectively. The aim of this study was to evaluate NIRS for measuring hepatic ICG clearance in an animal model of acute hepatic dysfunction.

Methods The study was conducted under a licence granted by the Home Office in accordance with the Animals (Scientific Procedures) Act 1986. New Zealand White rabbits (n = 36) underwent laparotomy and exposure of the liver. Total hepatic blood flow (THBF) was measured by transonic ultrasonic flowmeter probes. Liver microcirculation was measured by laser Doppler flowmeter (LDF). Hepatic ICG clearance was measured by NIRS. Six groups of animals were investigated: group 1, control; group 2, hepatic artery (HA) occlusion; group 3, portal vein (PV) partial occlusion; group 4, lobar ischaemia and reperfusion (IR) for 60 min respectively; group 5, inclusion of colchicine; and group 6, bile duct ligation (BDL). Hepatic ICG concentration was calculated by a curve-fitting technique, using a two-compartment model. α and β are the rate of ICG uptake and removal respectively.

Results

Group	LDF (flux)	THBF (ml min^{-1})	α (min^{-1})	β (min^{-1})
Control	236(22)	127(9)	1·85(0·51)	0·100(0·060)
HA occlusion*	216(16)†	115(8)	0·37(0·09)†	0·080(0·030)
PV occlusion*	176(22)†	75(6)	0·27(0·14)†	0·120(0·080)
IR*	195(11)†	129(5)	0·85(0·59)‡	0·020(0·006)‡
Colchicine	229(20)	122(9)	1·74(0·40)	0·030(0·010)‡
BDL	240(14)	132(5)	1·82(0·77)	0·002(0·001)‡

Values are mean(s.d.) (n = 6). *Values after occlusion or reperfusion. †P < 0·001, ‡P < 0·005

α significantly correlated with THBF (r = 0·68, P = 0·006) and parenchymal perfusion (r = 0·55, P = 0·005). β was significantly reduced by liver IR, colchicine and BDL.

Conclusion NIRS measurement of hepatic ICG concentration is a promising technique for assessing liver parenchymal dysfunction and may have important application in liver transplantation.

Exposure of peritoneal macrophages to carbon dioxide pneumoperitoneum suppresses function and diminishes anti-tumour cell cytotoxicity

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Background The safety of laparoscopic surgery for malignant disease has been questioned because of the incidence of port-site metastases and the possible increased risk of recurrence. Several experimental studies have demonstrated enhanced cancer growth following carbon dioxide laparoscopy. Possible mechanisms include a direct effect of carbon dioxide on tumour biology or an indirect effect on antitumour defences. Because of its anatomical location, the peritoneal macrophage plays a pivotal role in postsurgical immune responses. The effect of carbon dioxide pneumoperitoneum on peritoneal macrophage activation and antitumour cytotoxicity was examined.

Methods Rodent peritoneal macrophages (2×10^5 ml^{-1} in RPMI) were incubated in 95 per cent air/5 per cent carbon dioxide (control), 100 per cent helium or 100 per cent carbon dioxide for 3 h at 37°C. Following exposure, cells were stimulated with lipopolysaccharide (LPS) 1 µg ml^{-1} and tumour necrosis factor (TNF) α production was measured by enzyme-linked immunosorbent assay at 0 and 6 h. To assess cancer cell lysis, 5′-bromo-2′-deoxyuridine (BrdU)-labelled CC531s colon cancer cells were co-cultured for 18 h with gas-exposed peritoneal macrophages. DNA fragments in the supernatant were measured using anti-BrdU antibody and cell lysis expressed as a ratio to control.

Results

	Control	Helium	Carbon dioxide
Peritoneal macrophage TNF (pg ml^{-1})			
0 h	116·5(15·5)	61·7(27·1)	41·9(23·4)*
6 h	1085·5(98·7)	905·8(49·2)*	628·6(46·4)*‡
Relative cancer cell lysis	1·0	0·89	0·75†
Macrophage viability (%)	>90	>90	>90

Values are mean(s.d.). *P < 0·001 *versus* control; †P < 0·01 *versus* control; ‡P < 0·001 *versus* helium (one-way analysis of variance)

Conclusion Macrophage exposure to both helium and carbon dioxide caused a significant impairment in responsiveness to stimulation by LPS without affecting cell viability. Furthermore, carbon dioxide exposure caused significant attenuation of cancer cell lysis compared with controls. These data may have important implications for laparoscopy in the presence of intraperitoneal cancer cells.

Hepatocyte growth factor improves antigen-presenting capability of cultured human dendritic cells

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Background Although dendritic cells (DCs) are being used in clinical trials because of their potent ability to initiate T cell responses, difficulties isolating large numbers of DCs and a relative lack of knowledge about maximizing their ability to present antigen *in vivo* limit their use. Hepatocyte growth factor (HGF) is a cytokine which has powerful mitogenic, motogenic and morphogenic activities on numerous cell types. It was postulated that it might improve the yield and antigen-presenting ability of human blood-derived cultured DCs.

Methods Mononuclear cells were isolated from normal peripheral blood and depleted of contaminating non-precursor cells. Precursors were cultured in medium supplemented with optimal concentrations of granulocyte–macrophage colony-stimulating factor and interleukin 4 as determined in preliminary experiments. Cultures were maintained for 14 days before harvest of floating mature DCs for morphological and immunophenotypic analysis. Stimulatory ability was assessed using the mixed leucocyte reaction with stimulator:responder (S:R) ratios from 1:3 to 1:27. Experiments were performed in triplicate.

Responder cell type	Gelatin substrate	Gelatin absent
None	1143	802
Syngenic	2672	1768
Allogenic	12275*	5736

Responder cell type	HGF (ng ml^{-1})					
	0	0·1	0·5	2·5	5·0	7·5
None	915	850	823	1083	936	917
Syngeneic	2472	3276	3041	4246*	4130*	3824
Allogenic	10795	8902	9661	11306	12732*	9920

Results in c.p.m. for 1:27 S: R ratios. *$P<0\cdot01$ all *versus* gelatin absent

Results Culture of DC precursors on a 1 per cent gelatin substrate increased the ability of mature DCs to present syngeneic and allogeneic antigens ($P<0\cdot01$). Analysis of a concentration curve for recombinant human HGF showed optimal enhancement of stimulatory ability to be achieved at 5 ng ml^{-1}, which significantly increased syngeneic and allogeneic antigen-presenting ability ($P<0\cdot01$).

Conclusion Gelatin substrate significantly increases the stimulatory ability of cultured blood-derived human DCs. This effect is further increased by HGF supplementation. These modifications may improve the ability of DCs to present tumour antigen in clinical immunotherapeutic trials.

Activated matrix metalloproteinase 2 in human colorectal cancer

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Background Matrix metalloproteinase (MMP) 2 is a member of the matrix-degrading metalloproteinase family. It is released as a proenzyme predominantly by stromal cells and activated mainly at the tumour epithelial surface by membrane-type MMP. MMP-2 degrades type IV collagen in the extracellular matrix surrounding the tumour and is believed to play a critical role in cancer invasion and metastasis. The regulation of activation of MMP-2 is a key step during acquisition of invasive capacity. The aim of this study was to examine the activity of MMP-2 in colorectal cancer specimens compared with corresponding normal mucosa and its relation to Dukes stage.

Methods One hundred paired tumour and corresponding normal mucosa samples were taken from resected colorectal specimens. Gelatin zymography was performed and the amount of MMP-2 activity was quantitated by computer-assisted densitometry.

Results

Activated MMP-2 activity	Adenoma ($n=7$)	Dukes A ($n=15$)	Dukes B ($n=34$)	Dukes C ($n=44$)
T/N	1·39	2·46	3·10	3·08
Normal (%)	27	37	27	27
Tumour (%)	42	49	51	53

Values are median levels of activity. T, tumour; N, normal

Significantly more activated MMP-2 was found in tumour compared with normal mucosa ($P=0\cdot0001$). In each Dukes stage the ratio of the activated to the total MMP-2 was significantly increased ($P=0\cdot0001$). There was no significant difference between the different Dukes stages although there was an increasing trend toward the more advanced Dukes stage.

Conclusion These findings confirmed that activation of MMP-2 is increased in colorectal cancer. Inhibiting the activation of MMP-2 may prevent invasion and subsequent metastasis, and hence it may be an important future therapeutic target.

Early repair of parturition-related anal sphincter injury improves clinical and physiological outcome

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Background Obstetric injury to the anal sphincters may go unrecognized at the time of parturition and repair is often delayed until frank faecal incontinence develops. This study compared the outcome of 75 patients who had immediate anal sphincter repair (mean age 33 years) with 22 patients who underwent delayed overlapping anal sphincter repair, a mean of 10 years after first vaginal delivery (mean age 44 years).

Methods Patients were assessed for faecal incontinence (0–20 Pescatori score) and perineal pain before undergoing transanal ultrasonography and anal manometry to determine anatomical and physiological outcome.

	Pescatori score	Maximum resting pressure (mmHg)	Maximum squeeze pressure (mmHg)
Early repair	4·5(5·9)	44·6(24·6)	77·9(48·6)
Delayed repair	8·9(5·3)*	27·9(14·5)*	44·0(19·7)*

Values are mean(s.d.). *$P\leq0\cdot005$ *versus* early repair (*t* test)

Results Patients after early repair had significantly better symptomatic and physiological outcome than those having delayed repair. Early repair was associated with more ongoing perineal pain and faecal urgency than late repair. Ultrasonography revealed better anatomical repair after early operation.

Conclusion Early primary sphincter repair offers better outcome to patients with anal sphincter injury caused by traumatic vaginal delivery. This study highlights the need for early identification and repair of anal sphincter injury during parturition.

Homocysteine-mediated vascular injury as a putative mechanism of inflammatory bowel disease-associated atherothrombosis

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Background Mesenteric microvascular thrombosis and hyperhomocysteinaemia are recognized findings in inflammatory bowel disease (IBD). Homocysteine has a direct damaging effect on the endothelium rendering it thrombogenic. This study assessed the *in vivo* effect of homocysteine on microvasculature blood flow.

Methods Mesenteric postcapillary venules (2·8 μm) of Sprague–Dawley rats were superfused with bicarbonate-buffered solution (BBS) or rising concentrations of homocysteine. Group 1 (control) was superfused with BBS ($n = 10$), group 2 with homocysteine 10 μmol l^{-1} ($n = 10$) and group 3 with homocysteine 100 μmol l^{-1} ($n = 10$). Leucocyte–endothelial interaction was monitored by counting the number of adherent and migrating leucocytes. Red blood cell (RBC) velocity and leucocyte rolling velocity was also measured by intravital microscopy at baseline, and 10, 60 and 90 min after superfusion with homocysteine. Neutrophil expression of CD11a, CD11b and CD18 was determined by flow cytometry. Plasma homocysteine concentration was measured by fluorimetric high-pressure liquid chromatography. Endothelium morphology was studied using scanning electron microscopy. Groups were compared using analysis of variance and student's *t* test.

Results

	Leucocyte rolling velocity (μm s^{-1})		RBC rolling velocity (mm s^{-1})	
Time point	Group 2	Group 3	Group 2	Group3
Baseline	41	45	4	4
30 min	37	39	3	3
60 min	32	0	3	0
90 min	0	0	0	0

$P < 0{\cdot}005$ *versus* baseline

Microvascular thrombosis was evident by 90 min of homocysteine 10 μmol l^{-1} superfusion and at 60 min of homocysteine 100 μmol l^{-1} superfusion.

Conclusion This is the first direct evidence of the thrombotic effect of homocysteine *in vivo*; the effect is dose dependent. This may have implications for homocysteine as a causative factor in IBD-associated thrombosis.

Effect of essential fatty acid supplementation on local and systemic immune mechanisms in patients with ulcerative colitis

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Background Patients with ulcerative colitis have a variable and disordered alteration in host defences. Current therapy is of variable effectiveness and can have significant side-effects. Recent studies have demonstrated that dietary supplementation with essential fatty acids (EFAs) is immunosuppressive. Furthermore, it has been shown that EFA supplementation can improve disease activity in patients with ulcerative colitis. The aim of this study was to determine the effects of dietary supplementation with EFAs on key aspects of systemic and local immune function in patients with ulcerative colitis.

Methods Patients with extensive and active ulcerative colitis ($n = 30$), receiving standard therapy, were randomized to receive dietary supplementation with EFA (eicosapentaenoic acid 3·2 g day^{-1} and docosahexaenoic acid 2·4 g day^{-1}) or placebo (sunflower oil) for 6 months. Circulating levels of natural killer and lymphokine-activated killer cells (CD16 positive, CD56 positive, activated T cells (CD25 positive, T helper and T suppressor cells (CD4 positive and CD8 positive) were determined using fluorescein-activated cell sorter analyses. In addition, the levels of cytokines (interleukin (IL) 1 receptor antagonist, IL-2, IL-4, IL-6, IL-8, IL-10, IL-15, tumour necrosis factor α, interferon γ) in colonic washouts and serum from patients were measured using enzyme-linked immunosorbent assay techniques. These were documented before the start of treatment and at month 3 and month 6 of supplementation.

Results After 6 months of dietary supplementation with EFA or placebo there was a significant reduction in the circulating numbers of CD4-positive ($P < 0{\cdot}05$), CD16-positive ($P < 0{\cdot}005$) and CD56-positive ($P < 0{\cdot}05$) cells in patients receiving EFAs compared with those receiving placebo. Both circulating and colonic washout levels of IL-6, IL-8 and IL-10 were significantly lower in patients receiving EFAs compared with those in the placebo group ($P < 0{\cdot}05$).

Conclusion Dietary supplementation with EFAs in patients with ulcerative colitis results in a suppression in key aspects of systemic and local immune reactivity.

Moderate hyperhomocysteinaemia fails to exacerbate intimal hyperplasia

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Background Intimal hyperplasia is the rate-limiting factor determining long-term patency of revascularization procedures. Epidemiological data have implicated hyperhomocysteinaemia as a causative factor in graft intimal hyperplasia. To establish the direct biological link between hyperhomocysteinaemia and intimal hyperplasia, an animal model of hyperhomocysteinaemia was developed and the effect of hyperhomocysteinaemia on experimental intimal hyperplasia was studied.

Methods Three-month-old Sprague–Dawley rats (300 g) were randomized into four groups; group 1 ($n = 15$) was fed normal rat chow for 12 weeks; group 2 ($n = 10$) was fed a vitamin B6-, B12- and folate-deficient diet for 12 weeks; group 3 ($n = 10$) was fed a vitamin B6-, B12- and folate-deficient diet and succinylsulphathiazole (10 g per kg diet) for 12 weeks; and group 4 ($n = 10$) was fed normal rat chow and succinylsulphathiazole (10 g per kg diet) for 12 weeks. At 8 weeks, animals in the four groups underwent standardized balloon de-endothelialization injury of the left carotid artery using a size 2 Fogarty catheter. At 12 weeks, carotid arteries were harvested, perfusion fixed, histologically prepared and digitally analysed to measure cross-sectional areas of intima, media and lumen. Plasma homocysteine was measured using a fluorimetric high-performance liquid chromatography assay.

Results

	Folate (μg l^{-1})	B12 (ng l^{-1})	Homocysteine (μmol l^{-1})	Mean intimal area (mm^2)
Group 1	>20	1190	4(0)	0·197
Group 2	4	351	19(1)	0·201
Group 3	2	211	80(4)	0·199
Group 4	16	920	5(0)	0·198

Values are mean(s.d.). Groups were compared using analysis of variance and Student's *t* test

Moderate hyperhomocysteinaemia failed to exacerbate experimental intimal hyperplasia.

Conclusion Deficiency of folate and B12 inhibits DNA synthesis and therefore modulates homocysteine's mitogenic potential, providing a putative explanation for the failure to exacerbate intimal hyperplasia in this model. These data highlight the need for a genetically engineered animal model of hyperhomocysteinaemia to simulate the human disease.

Renal nitric oxide metabolism following infrarenal aortic cross-clamp-induced ischaemia–reperfusion injury

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Background The aims of this study were to investigate the influence of infrarenal aortic cross-clamping on glomerular filtration rate (GFR) and endogenous renal nitric oxide metabolism.

Methods Groups of male Wistar rats ($n = 6$) were subjected to infrarenal aortic cross-clamping for 30, 45 and 60 min. Following the ischaemic period the clamp was removed and the animals were maintained under anaesthesia for a further 60 min of reperfusion. A left nephrectomy was performed and the tissue was snap frozen for subsequent analysis. The GFR of the remaining kidney was measured on the second and seventh day after operation. Animals were killed on day 7 and the remaining kidney was harvested. Nitric oxide synthase (NOS) activity was measured in renal tissue by the conversion of [^{3}H]arginine to [^{3}H]citrulline in homogenates. GFR was determined using ^{99m}Tc DPTA. All procedures were performed with Home Office approval under the Animals (Scientific Procedures) Act 1986.

Results

Cross-clamp time	GFR (ml min^{-1})		NOS (pmol per mg per 45 min)	
	Day 2	Day 7	Day 1	Day 7
Control	2·25(2·04–2·42)	2·33(2·03–2·48)	13 (8–17)	12 (10–15)
30 min	1·62(1·47–1·82)*	1·73(1·65–1·83)*	55 (43–67)†	49 (38–53)†
45 min	1·53(1·45–1·64)*	1·63(1·64–1 69)*	71 (55–89)†	58 (25–62)†
60 min	1·45(1·37–1·57)*	1·49(1·44–1·63)*	91 (69–116)†	71 (55–97)†

Results are median (range). *$P<0{\cdot}05$, †$P<0{\cdot}01$ *versus* control (Mann–Whitney U test)

Conclusion Impairment of renal function following infrarenal cross-clamping is associated with an increase in endogenous renal nitric oxide metabolism. This response may be beneficial as it may maintain renal blood flow and oppose the effect of systemic vasoconstrictors released in response to this insult. Manipulation of this response may have beneficial effects during aortic surgery.

Taurine restores endothelial-dependent but not -independent dysfunction in young cigarette smokers

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Background Abnormal vasoactivity, manifesting as reduced vasodilatation or paradoxical vasoconstriction in response to physiological stress, is a feature of established vascular disease. Flow-dependent dilatation is known to be dependent on intact endothelial function. Cold pressor vasoactivity is thought to depend in part on endothelial vasodilator function and also on adrenergic stimulation. Using a non-invasive technique of measuring brachial artery diameter, the effect of cigarette smoking on both flow-mediated and cold pressor-induced arterial diameter changes was compared. It was postulated that cigarette smoking impairs endothelial-dependent and -independent functions. The effects of taurine, an antioxidant which has also been shown recently to upregulate constitutive nitric oxide production, on flow-mediated and cold pressor-induced arterial changes in smokers were also investigated.

Methods Eight healthy smokers and 11 non-smoking controls were studied. Right brachial artery diameter changes were measured using ultrasonography under baseline conditions, during reactive hyperaemia and at 1-min intervals for 10 min after immersion of the left hand in ice. Flow-mediated and cold pressor responses were reassessed in smokers after supplementation with taurine 1·5 g day^{-1} for 5 days.

Results Flow-mediated dilatation was observed in all control subjects, but was significantly impaired in smokers ($P<0{\cdot}005$). Oral supplementation of taurine markedly improved dilatation ($P=0{\cdot}005$), returning diameters back to those of controls. Cold pressor-induced vasodilation was present at 1 min in controls in contrast to smokers, in whom vasoconstriction was induced at this time point ($P=0{\cdot}02$). After taurine supplementation cold pressor-induced vasoconstriction was reduced ($P=0{\cdot}05$), but vasoactivity was not restored to that of controls.

	Non-smokers	Smokers	Smokers with taurine supplementation
Flow-dependent dilatation (mm)	0·37(0·09)	0·02(0·01)*	0·36(0·04)†
Cold pressor-induced vasoactivity (%)	4·2(5·0) (dilatation)	4·0(1·3)‡ (constriction)	0·5(1·9)§ (constriction)

Values are mean(s.d.). *$P<0{\cdot}005$ *versus* non-smokers; †$P=0{\cdot}005$ *versus* smokers; ‡$P=0{\cdot}02$ *versus* non-smokers; §$P=0{\cdot}05$ *versus* smokers

Conclusion These data confirm the presence of endothelial-dependent and -independent abnormal vasoactivity in otherwise healthy young smokers. Treatment of smokers' endothelium does not normalize the response of the blood vessel to stress. The failure to completely restore normal haemodynamics with taurine underscores the need to eschew cigarette smoking.

S-100 relates to hypoperfusion during carotid surgery

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Background Cerebral injury is rare during carotid endarterectomy (CEA). S-100, a sensitive indicator of neuronal injury, was measured in jugular bulb blood during CEA in 28 patients with greater than 70 per cent stenosis of the internal carotid artery. Cerebrovascular reactivity (CVR) to inhaled carbon dioxide was measured before operation.

Methods CEA was performed under general anaesthesia with blood pressure and end-tidal carbon dioxide controlled. Cerebral oxygen saturation (CsO_2) in the middle cerebral territory was measured by near infrared spectroscopy and middle cerebral artery blood flow velocity by transcranial Doppler (TCD). An intraluminal shunt was inserted if regional CsO_2 fell by more than 10 per cent and/or TCD fell by more than 80 per cent. Jugular bulb blood was sampled before carotid clamping, before and immediately after declamping and at 3 and 10 min later. S-100 was measured by immunoluminometric assay.

Results Initially the S-100 level was raised (normal level less than 0·12 μg l^{-1}; $P<0{\cdot}05$) and increased significantly during cross-clamping and further following declamping ($P<0{\cdot}01$). The single patient who suffered a postoperative stroke had the highest level of S-100 (1·9 μg l^{-1}). The fall in TCD on cross-clamping correlated weakly with subsequent S-100 level ($r_s=0{\cdot}4$, $P=0{\cdot}06$). There was no correlation between S-100 and ipsilateral CVR or severity of contralateral carotid stenosis.

Conclusion S-100 levels rise during CEA and relate to falls in regional blood flow on TCD. A high S-100 level during CEA may predict postoperative stroke.

	Preclamping	Predeclamping	On declamping	3 min after declamping	10 min after declamping
S-100 (μg l^{-1})	0·21 (0·08–0·32)	0·26 (0·12–0·42)*	0·36 (0·17–0·49)†	0·29 (0·17–0·41)†	0·24 (0·17–0·38)

Values are median (interquartile range). *$P<0\cdot05$, †$P<0\cdot01$ *versus* initially (Mann–Whitney *U* test)

Prevention of apoptosis in interferon γ-activated endothelial cells with heparin treatment

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Background Apoptosis is recognized to be of importance in a number of biological processes including cardiac allograft vasculopathy and rejection. A variety of signals can trigger apoptosis (e.g. Fas–Fas ligand binding). It has been suggested that major histocompatibility complex (MHC) class II may provide such a signal in macrophages. Given the ontogenetic relationship between macrophages and endothelial cells, it was investigated whether such signalling would cause endothelial cell apoptosis and if this could be prevented by heparin.

Methods Monolayers of human umbilical vein endothelial cells (HUVECs) were incubated for 96 h in endothelial cell culture medium with interferon (IFN) γ alone (to induce activation and expression of MHC class II) or combined with the low molecular weight heparin, dalteparin. Trypsinized cells were exposed to anti-MHC II monoclonal antibody or unrelated isotype control for 1 h at 4°C and apoptosis was assessed by flow cytometry using Annexin V–propidium iodide dual labelling.

Results Resting endothelial cells had low levels of apoptosis when stimulated with either anti-MHC class II or isotype control monoclonal antibody (mean(s.d.) 2·2(0·5) per cent). IFN γ-activated endothelial cells showed a five-fold increase in apoptosis (12–15 per cent) when treated with anti-MHC class II compared with isotype control monoclonal antibody (2·0(0·5) per cent). A dose-related reduction of IFN-γ-induced MHC class II expression to resting levels was observed on co-culture with dalteparin (37·5(2·5) nmol ml^{-1}). Dalteparin (37·5(2·5) nmol ml^{-1}) also abrogated the apoptosis (3·0(0·5) per cent) induced by anti-MHC class II monoclonal antibody in activated endothelial cells to near resting endothelial cell levels. The reduction in apoptosis correlated with the dose-dependent decrease in the expression of MHC class II measured by FACS analysis.

Conclusion This study demonstrates for the first time apoptosis induced in HUVECs by MHC class II signalling and its prevention by heparin treatment. These results have important implications for immune-mediated atherothrombotic processes and heparins used as an adjunctive treatment may prove to be useful in preventing graft vasculopathy and rejection.

Increased platelet activation and aggregation during carotid endarterectomy

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Background Carotid endarterectomy (CEA) is used widely in the management of patients with symptomatic carotid artery disease. However, there remains an unpredictable and unacceptable risk of perioperative stroke. Platelet activation and aggregation during and after CEA may be important determinants of perioperative stroke.

Methods Platelet activation and aggregation was measured by whole blood flow cytometry and aggregometry in the peripheral arterial blood of patients during CEA and 24 h after. Platelet activation was measured by surface expression of P-selectin as a marker for activation and degranulation, and the PAC-1 antigen as a marker of aggregation. Platelet aggregation was also measured using whole blood platelet aggregometry. Patients were kept on aspirin 75–150 mg until the day of surgery and received an intravenous bolus of 5000 units unfractionated heparin before clamping the carotid artery.

Results Thirty patients undergoing CEA were studied. There was a significant rise from the baseline expression of P-selectin (median 6·0 (range 0·1–18·0) per cent) after carotid clamping (10·3(0·8–48·9) per cent; $P<0\cdot0001$), clamp release (10·2(0·6–25·7) per cent; $P<0\cdot01$) and 1 h after surgery (8·8(0·7–49·2) per cent; $P<0\cdot05$). There was increased expression of PAC-1 from baseline (median 0·9 (range 0·0–25·2) per cent) after carotid release (4·8 (0–47·9) per cent; $P<0\cdot001$), clamp release (4·8 (0·2–33·4) per cent; $P<0\cdot01$) and 1 h after surgery (1·8 (0·1–49·0) per cent: $P<0\cdot05$). Using whole blood platelet aggregometry, there was a large increase in platelet aggregability from baseline (median 7·0 (range 0–43·4) per cent) after carotid clamping (73·3 (5·0–96·5) per cent; $P<0\cdot0001$), after clamp release (13·2 (2·0–55·6) per cent; $P<0\cdot05$) and 1 h after surgery (82·2 (11·9–95·3) per cent; $P<0\cdot0001$). Platelet indices of activation remained raised at 24 h (*P* not significant). Two patients in this study had a postoperative neurological deficit.

Conclusion Significant platelet activation and aggregation occurs early after dissection and the administration of heparin during CEA despite the current use of antiplatelet treatment. This novel finding suggests that further antiplatelet strategies may be indicated during carotid surgery to prevent thromboembolic complications.

Arterial flow alters concentrations of proteins providing the non-thrombogenic surface of saphenous vein

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Background Venous endothelium acts as an important non-thrombogenic surface. This property may be altered when vein is used as an arterial bypass graft. This study investigated (1) how the expression of the antithrombotic endothelial proteins thrombomodulin and nitric oxide synthase (e-NOS) alters when saphenous vein is exposed to arterial flow conditions and (2) the role of ion channels in transducing these responses.

Methods Freshly excised segments of human saphenous vein were perfused with Krebs' solution in an *ex vivo* bypass circuit with arterial (mean pressure 100 mmHg, 80 counts per min, mean(s.e.m.) shear stress 0·30(0·1) N m^{-2}) or venous (20 mmHg, 0·02(0·01) N m^{-2}) flow conditions for 90 min. In separate experiments the perfusate was supplemented with either calcium ionophore (A23187 0·5 μmol l^{-1}) or drugs to block the following ion channels: potassium (tetraethylammonium (TEA) 3 mmol l^{-1}), stretch-activated (gadolinium 10 μmol l^{-1}) and voltage-gated calcium (nifedipine 20 μmol l^{-1}). Endothelial concentrations of thrombomodulin, eNOS, tissue factor and tissue plasminogen activator were assessed by quantitative immunohistochemistry (per cent CD31) and Western blotting of endothelial cell lysates (ratio to von Willebrand factor) before and after flow circuit.

Results

	Thrombomodulin		e-NOS	
Flow conditions	Staining	Blotting	Staining	Blotting
Basal	68·4(6·0)	1·5(0·2)	50·0(5·6)	0·3(0·0)
Arterial alone	32·9(3·0)*	0·1(0·0)*	70·1(5·0)*	1·5(0·1)*
Arterial and TEA	43·4(4·0)*	0·3(0·0)*	47·0(3·0)†	0·2(0·1)†
Arterial and gadolinium	75·6(3·5)†	1·1(0·2)†	84·5(6·0)*	1·6(0·3)*
Arterial and nifedipine	78·0(4·0)†	1·3(0·1)†	55·8(3·1)	1·4(0·2)*
Venous and A23187	41·2(4·0)*	0·3(0·1)*	48·0(4·0)	0·3(0·0)

Values are mean(s.e.) immunostaining area and lysate density of epithelium (6–8 experiments). $^*P \le 0{\cdot}01$ *versus* basal; $^\dagger P \le 0{\cdot}01$ abrogation of arterial flow-induced change (paired t test)

There was scant endothelial staining for tissue factor in any circumstance except following arterial flow in the presence of nifedipine, when the immunostaining area increased from 3·0(0·4) to 8·5(0·7) ($P = 0{\cdot}01$) (confirmed by Western blotting). Tissue plasminogen activator could not be detected in the endothelium of any vein segments.

Conclusion Arterial flow causes rapid changes in saphenous vein antithrombotic proteins. The downregulation of thrombomodulin is mediated by calcium flux, while the upregulation of eNOS is potassium dependent. The increase in tissue factor in the presence of nifedipine may reduce the benefit of blockade of channels early after vein grafting.

Systemic factors and pre-existing venous intimal hyperplasia in the detection of at risk grafts

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Background The relevance of raised plasma lipoprotein (a), fibrinogen and homocysteine levels, and the presence of pre-existing venous intimal hyperplasia (IH) to the development of vein graft stenosis (VGS) has been disputed. This study investigated the association between these plasma factors, IH and outcome, and the value of these in selecting grafts at high risk of failure.

Methods Lipoprotein (a), fibrinogen and homocysteine levels were measured in each patient and a vein biopsy taken. Pre-existing IH was graded semiquantitatively (0, no IH; I, mild; II, moderate, III, severe). Patients underwent duplex graft surveillance.

Results Sixty-three grafts in 56 patients were recruited. Forty-seven were available for follow-up (mean postoperative period 15 (range 5–30) months). Patients with no pre-existing IH had significantly lower homocysteine levels than those with IH ($n = 50$, $P = 0{\cdot}007$, Mann–Whitney U test), but significantly higher lipoprotein (a) levels ($n = 50$, $P = 0{\cdot}012$). Twenty-four of the 47 grafts developed VGS. There was no association between VGS and age, sex, diabetes, or level or reconstruction. Mean plasma fibrinogen was higher, although not significantly so, in those with VGS (4·16 *versus* $3{\cdot}18\,\mathrm{g\,l^{-1}}$; $n = 45$, $P = 0{\cdot}09$). Grafts with grade II/III IH were significantly more likely to stenose than those with grade 0/1 ($n = 40$, $P < 0{\cdot}025$, χ^2 test). There was a highly significant association between patients with grade II/III IH and/or raised fibrinogen and VGS level ($n = 38$, $P < 0{\cdot}005$, χ^2 test).

Conclusion Plasma homocysteine levels correlate with the presence of pre-existing IH, which itself correlates with VGS. There is a marked relationship between the presence of raised plasma fibrinogen levels and pre-existing IH with the development of VGS, and these investigations may allow early identification of grafts requiring intense surveillance.

Heat shock protein 65 increases arterial contractility

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Background An association has been shown between raised serum antibody levels to 65-kDa heat shock protein (HSP 65) and vascular disease suggesting that HSP 65 might play a role in its pathogenesis. The aim of this study was to investigate the direct effects of HSP 65 on the vasculature.

Methods Male Dark Agouti rats were immunized with $200\,\mu$g HSP 65 in Freund's incomplete adjuvant (HSP group). Five rats were used as control group. The animals were killed at 6 and 10 weeks following immunization. Rings of thoracic aorta were assessed for contraction and relaxation in response to phenylephrine and acetylcholine using an organ bath technique. The distal thoracic aorta was fixed and stained to determine intima/media thickness and to detect proliferating cellular nuclear antigen (PCNA). T-helper (Th) cell type 1 and 2 status was also assessed using flow cytometry.

Results The HSP group showed increased contractility in response to phenylephrine compared with controls (mean(s.e.) maximum contraction $0{\cdot}701(0{\cdot}030)\,\mu$g ($n = 9$) *versus* $0{\cdot}533(0{\cdot}029)\,\mu$g ($n = 5$); $P = 0{\cdot}004$, analysis of variance, Bonferoni/Dunn). The dose–response curve for acetylcholine was not significantly different. Controls reached 93 per cent maximal relaxation and rats in the HSP group 92 per cent suggesting intact endothelial nitric oxide synthesis. No significant difference could be found in intima/media thickness between the two groups (control group: intimal, $3{\cdot}8\,\mu$m; media, $80{\cdot}5\,\mu$m *versus* HSP group: intima, $3{\cdot}8\,\mu$m; media, $78{\cdot}0\,\mu$m). Staining for PCNA showed no difference between the groups. Cytokine expression was shifted from Th1 towards a Th2 status.

Conclusion This study has shown a change in vasoactivity produced by immunization with HSP 65. This novel finding may have implications for understanding the aetiology of vasospastic disorders and may give new ideas for possible therapeutic strategies such as the use of Th1 adjuvants in patients with vascular disease.

Systemic inflammatory response syndrome inhibits neutrophil apoptosis

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Background The systemic inflammatory response syndrome (SIRS) is a massive systemic proinflammatory reaction that may lead to the development of multiple organ dysfunction syndrome (MODS). MODS affects as many as 40 per cent of critically ill patients and remains the leading cause of death in the intensive care unit (ICU). Failure of the activated neutrophil to undergo apoptosis when its actions are no longer required, and thus failure to terminate the acute inflammatory response, has been proposed as a precipitant of SIRS. The aim of this study was to define definitively the effects of SIRS on neutrophil apoptosis.

Methods Patients who fulfilled established criteria for SIRS had whole venous blood harvested on admission to the ICU. The control group consisted of healthy volunteers. Platelet poor plasma (PPP) and neutrophils were isolated by dextran sedimentation and Ficoll gradient centrifugation. Neutrophils were suspended in RPMI supplemented with 10 per cent autologous PPP. Neutrophil apoptosis was quantified by immunofluorescence flow cytometry of annexin-V binding to phosphatidylserine residues on apoptotic cells and apoptosis was confirmed by morphology. To confirm if the observed inhibition of neutrophil apoptosis in patients with SIRS was secondary to a plasma mediated factor, healthy control neutrophils were co-cultured with PPP from patients with SIRS and apoptosis quantified. Approval for the study was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

Results

	Neutrophil apoptosis (%)		
Culture time (h)	Control neutrophils in control PPP	SIRS neutrophils in SIRS PPP	Control neutrophils in SIRS PPP
1	7·6(0·5)	8·9(0·2)	3·5(0·5)
12	65·2(6·6)	18·9(9·0)*	40·9(4·8)*
24	90·8(10·0)	45.5(15·2)*	60·5(13·1)*

Values are mean (s.e.m.). *$P<0{\cdot}05$ (Student's t test)

Conclusion These results show for the first time that in patients with established SIRS neutrophil apoptosis is significantly inhibited. This appears to be plasma mediated as culture of healthy neutrophils with PPP from patients with SIRS significantly inhibited neutrophil apoptosis. Therapeutic regulation of neutrophil apoptosis in patients with SIRS may provide exciting new therapeutic strategies capable of modulating the disease process and limiting host tissue injury.

Defective cleavage of neutrophil FcγRIIIb receptor in postoperative sepsis may lead to altered phagocytosis

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Background The authors reported previously that the glycan phosphatidyl inositol (GPI)-linked neutrophil (PMN) receptor FcγRIIIb (CD16) is overexpressed in patients who develop postoperative sepsis and that this overexpression is due to defective cleavage of the GPI linkage. In this study it was determined whether receptor overexpression influences calcium influx which is responsible for PMN phagocytosis and to date attributed to CD32 stimulation alone.

Methods Sixty-five patients (34 men; mean age 53 (range 35–89) years) undergoing surgery for benign and malignant gastrointestinal disease were studied; 12 had a septic postoperative course. PMNs stimulated by monoclonal anti-CD16 and anti-CD32 antibody had cytosolic free calcium changes measured in a calcium-free and calcium-enriched medium by dual-wavelength fluorimetry of cytosolic fura-2-AM using excitation wavelengths of 340 and 380 nm. Phagocytosis was quantitated by confocal microscopy and flow cytometry and the results expressed as mean phagosomes per cell.

Results Phagocytosis was less in the overexpressers (three *versus* nine phagosomes per cell, septic *versus* non-septic; $P<0{\cdot}01$, Mann–Whitney U test). Calcium influx increased following stimulation with CD32; however, when both receptors were stimulated together the increase was significantly prolonged in patients without sepsis (80 *versus* 55 s; $P<0{\cdot}001$, Mann–Whitney U test) and was quantitatively less in patients with sepsis (210 *versus* 250 nmol l^{-1}; $P<0{\cdot}01$, Mann–Whitney U test). Receptor overexpression was therefore associated with decreased phagocytic ability and a reduction in simulated calcium influx.

Conclusion These results support the suggestion that molecular therapy aimed at altering the non-cleavable receptor or re-inserting active native CD16 may reduce postoperative sepsis.

Anti-interleukin 10 therapy restores survival in postburn injury sepsis

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Background Injury induces T cell anergy which has been shown to correlate with susceptibility to sepsis. The aim of this study was to investigate the role of anti-interleukin (IL) 10 in reversing or preventing the immune suppression associated with burn injury, in an *in vivo* model.

Methods Eighty-four male A/J mice were randomized to receive under anaesthesia a 25 per cent scald burn or sham burn. All animals were further randomized to receive 250 μg either anti-IL-10 monoclonal antibody or control rat immunoglobulin (Ig) G on days 1, 2, 3 or 7 following injury. Ten days following injury animals underwent caecal ligation and puncture under anaesthesia. The optimal timing of anti-IL-10 antibody in preventing lethal shock after trauma was identified in an antigen-specific model, in which mice were immunized subcutaneously with 100 μg TNP-haptenated ovalbumin in incomplete Freund's adjuvant before sham or burn injury. On day 10 animals were killed to obtain spleen cells. *In vitro* cytokine production by total splenocytes in response to therapy on days 1, 2, 3, 5 and 7 was then analysed.

Results Burn-injured mice treated with anti-IL-10 monoclonal antibody had a significantly better survival following caecal ligation and puncture compared with mice treated with IgG ($P<0{\cdot}05$; log rank test). Early administration of anti-IL-10 antibody after injury provided the best opportunity for reversal of immune suppression while late administration proved lethal. Anti-IL-10 monoclonal antibody given on days 1, 2 and 3 significantly increased TNP-haptenated ovalbumin-specific T-helper 1 and T-helper 2 cytokine production in burn-injured mice compared with burnt mice that received IgG ($P<0{\cdot}01$; Student's t test). Later administration of anti-IL-10 antibody on day 7 after burn injury resulted in a significant increase in T-helper 1 cytokine, interferon γ, production only ($P<0{\cdot}01$; Student's t test).

Conclusion In this model early neutralization of IL-10 after burn injury prevented susceptibility to death by sepsis. At later time points following burn injury IL-10 may have a protective role. It is proposed that early administration of anti-IL-10 monoclonal antibody may prove beneficial as a therapy in the management of injury-induced immune suppression in the clinical setting.

Injury primes naive T cells for an augmented T-helper 1 response

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Background The authors have shown previously that post-traumatic immune suppression correlates with diminished T-helper (Th) 1 cell function in an animal model of burn injury. This occurred when mice were given antigen at the time of injury, indicating that burn injury can influence the development of antigen-specific T cell responses *in vivo*. To distinguish the effect of injury on naive *versus* antigen-activated T cells *in vivo*, burn injury studies were performed using AND and DA11.10 mice which express transgenic T cell receptors specific for pigeon cytochrome c (PCC) or ovalbumin (OVA) respectively. This approach allowed assessment of whether injury can alter T cells that do not have the capacity to respond to self-tissue antigens (naive T cells).

Methods Groups of four to five AND or DO11.10 transgenic mice underwent a 25 per cent scald burn injury or sham injury under anaesthesia, in accordance with local ethics committee guidelines. Seven days later, lymph node cells were harvested and stimulated with OVA (DO11.10 mice) or PCC (AND mice) to measure antigen-induced proliferation and cytokine production. To study the effect of burn injury on antigen-activated T cells, similar studies were performed using groups of four transgenic mice which were immunized subcutaneously with PCC or OVA on day 0.

Results Antigen-induced proliferation of lymph node cells from control and burn-injured mice was similar, but burn injury primed the naive T cells to produce a sevenfold higher level of interferon (IFN) γ (mean(s.d.) 1660(148) *versus* 238(29) units ml^{-1}; $P<0{\cdot}01$, *t* test). Increased production of Th2-type cytokines was not observed. Unexpectedly, the T cell receptor transgenic mice that were immunized with PCC or OVA on day 0 all died within 3 days after injury and immunization and had increased serum levels of IFN-γ. Control mice had a normal low mortality rate.

Conclusion Burn injury primes naive T cells to produce enhanced levels of IFN-γ upon antigen stimulation. This contrasts with authors' previous reports demonstrating that burn injury leads to a pronounced downregulation of Th1 cell function in immunized non-transgenic A/J mice. These findings support the hypothesis that the downregulation of Th1 cell function seen after burn injury may be dependent upon antigen activation and may be preceded by an augmented Th-1-type response with the potential to cause systemic inflammation.

Soluble P-selectin moderates complement-dependent injury

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Background P-selectin is an adhesion molecule expressed on activated endothelial and platelet surfaces. The function of the short consensus repeats (SCRs) of P-selectin, homologous with the SCRs of complement protein, is largely unknown. In an established murine model of intestinal ischaemia–reperfusion, where local injury is mediated by the classical complement pathway, it was hypothesized that the SCRs of soluble P-selectin would moderate the complement component of the inflammatory response.

Methods Mice deficient in P-selectin (P−/−), wild type (P+/+) and P−/− reconstituted with P+/+ platelets underwent 40 min of intestinal ischaemia and 4 h of reperfusion. The ^{125}I-radiolabelled albumin ratio in dry gut and bronchoalveolar lavage compared with blood was used to assess intestinal and pulmonary permeability respectively. Liver injury was assessed by determining serum alanine aminotransferase (ALT). *In vitro* experiments were set up to examine the role of soluble P-selectin on complement activity. Animals used in this study were maintained in accordance with the guidelines of Harvard Medical School.

Results

	P+/+	P−/−	P−/− +platelets	P+/+ Sham	P−/− Sham
Gut permeability (*n* = 12)	1·2(0·0)	1·2(0·1)	1·0(0·1)	0·4(0·0)	0·5(0·0)
Lung permeability (*n* = 12)	50·2(4·2)	50·0(3·2)	32·0(3·5)	23·7(0·7)	23·3(1·5)
ALT (units l^{-1})	60·0(4·6)	177·0(19·3)	77·0(7·7)	44·0(5·0)	36·0(1·2)

Values are mean(s.e.m.)

P−/− mice had similar local gut and lung injury but worse liver injury than wild type P+/+ mice. When reconstituted with P+/+ platelets, P−/− mice had a significant decrease in both local and remote injury compared with non-reconstituted *P*−/− mice. *In vitro* studies of complement activity (CH50 assay) showed that soluble P-selectin at a concentration of 20–25 ng ml^{-1} inhibited classical but not alternative CH50 by 50 per cent. CH50 was significantly reduced by 76 per cent in both P+/+ and P−/− animals, but by only 36 per cent in P−/− animals reconstituted with P+/+ platelets.

Conclusion Soluble P-selectin moderates complement-dependent injury by limiting activation of the classical pathway in murine intestinal ischaemia–reperfusion.

Central venous catheter-related sepsis: DNA fingerprints left at the scene

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Background Central venous catheters are the most common source of nosocomial staphylococcal septicaemia. Coagulase-negative staphylococci (CNS) are skin commensals regarded as the source of catheter contamination in the majority of cases of catheter-related sepsis (CRS). More than 30 genotypically distinct species of CNS exist, and the purpose of the study was to confirm their source and route of access in CRS by the use of pulsed field gel electrophoresis (PFGE) DNA fingerprinting. CRS was defined as a positive catheter culture and associated peripheral bacteraemia with the same organism.

Methods In patients with confirmed CRS, skin entry site, control skin site, hub, extraluminal and endoluminal surfaces of the central venous catheter and peripheral blood were cultured; colonies from each site were subjected to PFGE.

Results Sixty cases of CRS were diagnosed over a 2-year period. Twenty-one (35 per cent) were due to CNS, but only 16 of these met the criteria for CRS using DNA fingerprinting. In the other five cases the CNS isolates from the catheter did not match the peripheral blood cultures. Skin entry sites and hub cultures matched catheter samples in only five and eight cases respectively. In seven cases the CNS causing the CRS were not isolated from the patient's own skin. Extraluminal and endoluminal colonization occurred in 12 and 16 of 16 respectively; endoluminal colony counts were significantly greater than extraluminal counts ($P<0{\cdot}01$).

Conclusion Central venous catheters are often colonized by sources other than the patient's skin. This probably represents poor aseptic technique when handling the catheter. Furthermore, regardless of the route by which the bacteria gain access, endoluminal colonization appears highly significant in the development of CRS.

Haemostatic function of fibrinogen-impregnated collagen following the addition of antibiotics

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Background Fibrin sealants are increasingly used in trauma surgery. The addition of antibiotics to liquid fibrin sealants may inhibit their haemostatic function, but the effect on dry preparations is unknown. This study evaluated the effect of presoaking fibrinogen-impregnated collagen (FIC) in an antibiotic solution on its haemostatic properties in a model of splenic trauma.

Methods Under general anaesthesia four 5-cm incisions were made in the spleen of six pigs. Wounds were covered by a 6 cm × 3 cm steel of either (1) dry FIC, (2) FIC soaked in 1 ml saline or (3) FIC soaked in 1 ml rifampicin 60 mg ml^{-1}. A fourth wound acted as untreated control. Systemic levels of rifampicin were measured hourly for 6 h after trauma using a *Staphylococcus aureus* inhibition assay. Levels of antibiotic in tissue removed at autopsy were measured using the same assay. Studies were authorized under the Animals (Scientific Procedures) Act, 1986.

Results

	Bleeding time (min)	Blood loss (ml)
Control	16(1)	112(21)
FIC dry	9(1)*	39(12)*
FIC–saline	9(1)*	43(11)*
FIC–antibiotic	10(1)*	32(4)*

Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* control (analysis of variance)

Concentrations of rifampicin greater than minimal inhibitory concentration were consistently present in systemic blood from 45 min after injury until the termination of the experiment after 6 h. At autopsy antibiotic was demonstrated in spleen and liver samples.

Conclusion Presoaking FIC in antibiotic had no significant effect on its haemostatic properties. The technique may allow local and systemic delivery of antibiotics in abdominal trauma and be of benefit in damage control surgery, especially in patients with contamination of visceral organs.

Vitamin C reduces ischaemia–reperfusion-induced pulmonary injury

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Background Ischaemia–reperfusion (I–R) induces a neutrophil-mediated oxidant injury. This is exacerbated by reduced concentrations of antioxidants such as vitamin C in cardiovascular patients. The aim was to evaluate vitamin C supplementation in the prevention of I–R-induced lung injury.

Methods Sprague–Dawley rats ($n = 6$ per group) were randomized into control, I–R and I–R pretreated with vitamin C (3·3 g over 5 days) groups. I–R injury was induced by 30 min of infrarenal aortic cross-clamping and 120 min of reperfusion. Pulmonary microvascular injury was measured by bronchoalveolar lavage (BAL) protein concentration, pulmonary neutrophil infiltration by tissue myeloperoxidase (MPO) activity and BAL neutrophil counts (BAL PMN). In a second experiment ($n = 5$ per group) neutrophil respiratory burst activity was measured in control and vitamin C groups.

Results

	BAL protein	BAL PMN	MPO
Control	169(25)	7·3(0·6)	5·4(0·6)
I–R	434(80)*	22·3(3·0)*	8·2(0·6)*
I–R + vitamin C	196(33)†	10·2(0·9)†	5·1(1·0)†

Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* control; †$P < 0{\cdot}05$ *versus* I–R (analysis of variance)

I–R resulted in a significant increase in both microvascular leakage (BAL protein) and neutrophil infiltration (BAL PMN, MPO). Pretreatment with vitamin C attenuated both parameters. Neutrophil respiratory burst activity was reduced in the vitamin C group (mean(s.e.m.) 13·0(0·3)) compared with the control group (19·0(1·9)) ($P < 0{\cdot}02$).

Conclusion These data suggest that oral vitamin C therapy protects against I–R-induced lung injury, possibly by attenuating neutrophil respiratory burst activity.

Lipopolysaccharide increases immune and tumour cell production of vascular endothelial growth factor *in vivo* and *in vitro*

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Background Vascular endothelial growth factor (VEGF) is a potent angiogenic cytokine that stimulates the growth and differentiation of endothelial cells. Lipopolysaccharide (LPS) is a bacterial cell wall constituent and is ubiquitously present in air. The authors have shown previously that open surgery results in increased metastatic growth and serum VEGF level, and hypothesized that LPS mediates these effects. In this study the effect of LPS on immune and tumour cell production of VEGF was examined *in vitro* and in a murine model of metastatic disease.

Methods Sixteen Balb/c mice were injected with 10^5 4T1 mammary adenocarcinoma cells by tail-vein injection. On day 14 the animals received an intraperitoneal injection of saline or LPS 10 μg. Plasma LPS levels were examined by the *Limulus* amoebocyte lysate assay and serum VEGF by enzyme-linked immunosorbent assay (ELISA). Human monocytes were isolated, matured to macrophages and activated with interferon γ 1000 units ml^{-1}. Monocyte-derived macrophages (MDMs) and 4T1 tumour cells were incubated with LPS for 24 h. VEGF production was assayed by ELISA and VEGF messenger RNA (mRNA) was assessed by reverse transcriptase–polymerase chain reaction.

Results LPS injection resulted in a significant increase in serum VEGF level compared with that in animals receiving a saline injection ($P < 0{\cdot}002$). Levels of plasma LPS correlated with serum VEGF levels ($r = 0{\cdot}967$). *In vitro*, VEGF production by both human macrophages and 4T1 tumour cells ($n = 3$) was significantly increased by treatment with LPS 0·1–10 μg ml^{-1} ($P < 0{\cdot}05$, analysis of variance). The VEGF mRNA level in MDMs was increased in response to LPS 1–100 ng ml^{-1}.

Conclusion Lipopolysaccharide increases VEGF at both the mRNA and protein level *in vitro*. *In vivo*, LPS injection results in an increased circulating VEGF level. LPS, through the induction of VEGF, is therefore a potential angiogenic and metastatic factor in breast cancer.

Artificial neural networks for prediction of outcome following surgery for gastric cancer

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Background An artificial neural network (ANN) is a form of computer artificial intelligence that is able to learn non-linear causal relationships between established data and use this knowledge to answer questions about data to which it has not been exposed. It was decided to compare a neural network analysis with the traditional statistical approach for the prediction of outcome following surgery for gastric cancer.

Methods ANNs were designed with 60 input variables in the first layer, 0, 2, 3, 4, 5, 6, 7, 15, 20, 25 or 30 hidden 'neurones' in the second layer and a simple positive/negative output. Data from 183 patients were used: 133 to train and 50 to validate each ANN for the prediction of death at 12 months. The neural networks were then compared against traditional multivariate analysis on ten randomly selected validation data sets.

Results The ANNs achieved a mean sensitivity of 0·62 (range 0·61–0·65) and a specificity of 0·77 (range 0·73–0·79) with a mean overall accuracy of 0·71 (95 per cent confidence interval (c.i.) 0·57–0·83) as opposed to the traditional multivariate analysis which achieved a mean sensitivity of 0·56 (range 0·43–0·79) and specificity of 0·68 (range 0·52–0·85) with a mean overall accuracy of 0·62 (95 per cent c.i. 0·49–0·75). There was

no statistically significant difference between the two methods of analysis although the ANNs were significantly more robust and consistent in their predictions.
Conclusion The failure to significantly improve on the accuracy of the traditional linear statistical methods is due to either too small a learning set or too simple a mathematical problem. This accepted, in practical terms, ANNs are able to provide a more consistent method of prediction of outcome following gastric cancer surgery.

Antiselectin therapy decreases survival in a murine model of acute peritonitis

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Background The selectin family of adhesion molecules is involved in initial neutrophil–endothelial binding, resulting in neutrophil migration at inflammatory sites. Antiselectin therapy appears to be a logical means of reducing neutrophil-mediated injury seen in the systemic inflammatory response syndrome. Prolonged inhibition of neutrophil function, however, may in theory be detrimental to survival in the presence of bacterial sepsis. The aim of this work was to study the effect of antiselectin therapy in an animal model of sepsis.
Methods Acute peritonitis was induced by caecal ligation and puncture in mice. Mortality rates were studied in (1) wild-type mice, (2) mice pretreated with P-selectin antibody, (3) mice pretreated with L-selectin antibody, (4) those pretreated with the selectin counter receptor, soluble P-selectin glycoprotein ligand 1, (5) mice deficient in P-selectin (P −/−) and (6) P −/− deficient mice pretreated with L-selectin antibody. In additional studies, neutrophil migration was assessed in peritoneal lavage fluid harvested at 0, 1, 3 and 6 h following injury. Animals used in this study were maintained in accordance with the guidelines of the Harvard Medical School.
Results The mortality rate at 72 h for wild-type mice was 60 per cent; for all other pretreated and deficient animals the mortality rate was 100 per cent ($P<0{\cdot}05$). The peritoneal lavage neutrophil count was significantly reduced at 3 and 6 h in pretreated and deficient animals compared with wild-type mice ($P<0{\cdot}05$).
Conclusion These data show that peritoneal neutrophil migration in a murine model of acute peritonitis is P- and L-selectin dependent. Inhibition of P- or L-selectin decreased survival by reducing neutrophil migration into the peritoneum.

Contribution of mesothelial cells to the peritoneal inflammatory response

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Background Intra-abdominal sepsis produces a peritoneal cytokine response with local and systemic effects. Classically, the early cytokines interleukin (IL) 1β and tumour necrosis factor (TNF) α, and their naturally occurring antagonists, IL-1 receptor antagonist (IL-1RA) and soluble TNF receptor (sTNF-R), are secreted by activated peritoneal macrophages. The role of mesothelial cells in the peritoneal cytokine response remains ill defined. The role of peritoneal mesothelial cells in the production of IL-1β and TNF-α and their antagonists IL-1RA and sTNF-R (type 1 and type 2) was investigated.
Methods Primary mesothelial cultures were established from samples of greater omentum (ethics committee approved) and characterized by immunohistochemistry. Confluent cultures or intact pieces of omentum were activated with lipopolysaccharide 10 ng ml^{-1} for 2 h and analysed by semiquantitative reverse transcription–polymerase chain reaction using primers for IL-1β, TNF-α, IL-1RA, sTNF-R (type 1 and type 2) and the housekeeper gene glyceraldehyde-3-phosphodehydrogenase.
Results Activated mesothelial cells showed an upregulation of cytokine messenger RNA. A similar but more pronounced effect was seen with intact omental samples.

Sample	IL-1β	IL-1RA	TNF-α	sTNF-R (type 1)	sTNF-R (type 2)
Mesothelial ($n=8$)	40 (30–80)	50 (10–90)	40 (10–70)	30 (0–50)	10 (0–30)
Omentum ($n=10$)	90 (70–100)	50 (20–120)	130 (20–140)	50 (30–120)	100 (60–120)

Values are median (interquartile range) percentage increase compared with controls. All $P<0{\cdot}05$ *versus* controls (Mann–Whitney U test)

Conclusion Activated mesothelial cells make a significant contribution to the peritoneal inflammatory response and may represent a suitable target for modulating the immunological response to abdominal sepsis.

High-dependency units improve outcome

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Background Only a minority of hospitals in the UK have high-dependency units (HDUs). The outcome of patients undergoing major colorectal surgery was compared with regard to HDU utilization.
Methods Two groups of patients were assessed. The non-HDU group underwent major colorectal surgery over a 5-month period in a hospital without an HDU and returned to a general ward after operation. The HDU group were managed initially in an HDU following operation. Data collected included the Physiological and Operative Severity Score for EnUmeration of Mortality and morbidity (POSSUM) score, calculated risk of morbidity and death, length of stay, complications and deaths.
Results The non-HDU group comprised 40 patients with a median age of 68 (range 26–94) years. POSSUM scoring revealed a median physiological score of 19 (range 13–33) and a median operative score of 16 (range 10–29). Thirty-one patients experienced complications compared with the 15·2 expected, giving an observed : expected (O : E) ratio of 2·04. Four patients died compared with an expected 3·4 (O : E 1·18). The median postoperative stay was 14 (range 5–55) days with 26 patients staying longer than predicted. There were 48 patients in the HDU group, of median age 70 (range 16–87) years. Median physiological score was 19 (range 13–46) and median operative score was 14 (range 10–28). Complications occurred in 18 (14·7 expected; O : E 1·22). There were two deaths (4·35 expected; O : E 0·46). Median stay was 10 (range 3–60) days and 26 patients exceeded predicted stay.
Conclusion Patients managed in the HDU after operation did better than those returned to a general ward. Using the POSSUM system to obtain expected outcomes based on severity of illness allows valid comparison between units.

Regional management of infantile hypertrophic pyloric stenosis

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Background It has been suggested recently that infantile hypertrophic pyloric stenosis (IHPS) should be managed only by specialist paediatric surgeons. However, the authors believe that the majority of these infants may be managed in a well equipped regional centre, with transfer to specialist paediatric surgical centres reserved for complex cases.

Methods The national Hospital Inpatient Enquiry database was queried to identify all 70 cases of IHPS with a home address within a single administrative region (population 320 000), between January 1991 and December 1996. Chart review furnished the necessary demographic and clinical details. Of the 70 infants identified, three were treated primarily outside of the region and the remaining 67 patients were initially assessed in the regional general hospital (RGH). Four were subsequently referred to a specialist paediatric surgical hospital because of prematurity ($n=1$), low birth weight ($n=1$), large capillary haemangioma ($n=1$) or because severe metabolic derangement rendered management more complex.

Results Among the 63 infants (90 per cent) treated primarily in the RGH, 53 (84 per cent) were male, 20 (32 per cent) were first born and only six (10 per cent) had a positive family history. Median age at diagnosis was 34 (range 13–90) days. The clinical suspicion of IHPS was confirmed by test feed in 47 cases, and using barium meal and ultrasonography in 14 and two patients respectively. Ramstedt's pyloromyotomy was performed on the next available elective operating list, following correction of electrolyte abnormalities. Enteral intake was resumed after 24 h. There were no negative laparotomies or perioperative deaths. Mean postoperative stay was 8 (range 2–42) days. After operation, vomiting occurred in 14 patients; this was self limiting in nine patients and due to gastro-oesophageal reflux in a further four. One infant was transferred for repeat pyloromyotomy. There were three significant wound infections and one case of wound dehiscence. Twenty patients (32 per cent) had significant co-existing conditions.

Conclusion These data show that the majority of infants with IHPS may be safely managed exclusively in regional centres with transfer to specialist paediatric surgical centres reserved for high-risk cases. The management of IHPS at a regional level has important implications and opportunities for surgical training.

Expression of *bcl*$_{XL}$ correlates with survival in pancreatic cancer

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Background The *bcl-2* family of genes is critical in the regulation of apoptosis and may inhibit (*bcl-2, bcl*-$_{XL}$) or promote (*bax, bak, bcl*-$_{XS}$) cell death. Overexpression of *bcl-2* and reduced expression of *bax* has been reported in a number of tumours where it is associated with resistance to radiochemotherapy and a poorer prognosis.

Methods The expression of *bcl-2, bax, bcl*-$_{X}$, *bak* and *p53* was determined in formalin-fixed paraffin wax-embedded archival tissue specimens of adenocarcinoma of the pancreas ($n=24$; median age 59 (range 41–76) years), ampullary cancer ($n=7$; median age 65 (range 59–73) years) and chronic pancreatitis ($n=7$; median age 48 (range 31–56) years) by immunohistochemistry using specific monoclonal (*bcl-2, p53*) and polyclonal (*bax, bcl*-$_{X}$, *bak*) antibodies. Normal pancreatic tissue ($n=7$) was obtained from organ transplant donors. Statistical analysis was by Fisher's exact test and Kaplan–Meier (log rank) method.

Results In the normal pancreas *bcl-2, bax, bcl*-$_{XL}$ and *bak* were expressed predominantly in ductal epithelial cells. Expression was not significantly different in chronic pancreatitis. Eleven of 24 pancreatic and four of seven ampullary cancers had overexpression of *p53* ($P<0\cdot03$). Pancreatic cancer was associated with absent expression of *bcl-2* in all 24 specimens ($P<0\cdot001$). The intensity of immunostaining for *bax, bcl*-$_{XL}$ and *bak* was reduced in 18, 14 and 24 of 24 cases respectively ($P<0\cdot001$). Similar changes were observed in ampullary cancer. In pancreatic cancer, strong expression of *bcl*-$_{XL}$ was associated with a median postoperative survival of 171 days compared with 598 days for weak expression ($P<0\cdot01$). Median survival time was 365, 337 and 259 days for strong, weak and negative *bax* expression respectively (P not significant). No correlation was observed between the expression of apoptotic genes and tumour stage or differentiation.

Conclusion Expression of the *bcl-2* family of apoptosis-regulating genes is disrupted in pancreatic and ampullary cancer. A relative overexpression of apoptosis inhibiting *bcl*-$_{XL}$ may result in a poorer prognosis in pancreatic cancer.

Oxidative stress in patients receiving early enteral nutrition following operations for hepatic or pancreatic disease

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Background Oxidative stress and septic complications are an integral part of serious inflammatory conditions including serious sepsis and major blunt trauma. Aggressive nutritional support in the form of total enteral nutrition (TEN) is known to attenuate this phenomenon possibly by reducing translocation of endotoxin or micro-organisms from the gut lumen into the systemic circulation. There is a dearth of such data in respect of patients recovering from major abdominal operations. The aim of this study was to investigate the effect of major hepatic and pancreatic operations on oxidative stress and to ascertain if early enteral nutrition would have a beneficial effect.

Methods Lipid peroxidation was measured as an index of oxidative stress by quantifying thiobarbituric acid reactive substances in the plasma of 37 patients undergoing hepatic or pancreatic operations for benign or malignant disease. This was measured before operation and again on day 3 and day 7 after operation. Patients were randomized to receive no nutritional support or TEN immediately after operation.

Results

		Thiobarbituric acid reactive substances (μg l^{-1})		
Feed	*n*	Preop.	Day 3	Day 7
Control	22	3·8(2·8)	4·0(1·8)	4·4(2·1)
TEN	15	5·1(4·6)	5·7(4·5)	5·9(3·0)
P		0·29	0·13	0·08

Values are mean (s.d.)

Conclusion Although TEN is safe and well tolerated in patients who have undergone hepatic and pancreatic operations there is no advantage in terms of attenuation of oxidative stress.

Mechanisms of bradykinin-induced contraction of human gallbladder muscle strips *in vitro*

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Background Bradykinin (BK) is an inflammatory mediator. The classification of two BK receptors (B1 and B2) is widely accepted. Several experiments suggest further classes of BK receptors. The aim of this study was to determine the effects of BK on human gallbladder motility *in vitro* and to investigate receptor subtypes which mediate the BK response.

Methods Gallbladders were obtained from patients undergoing cholecystectomy for gallstone disease and from patients undergoing resection for pancreatic or hepatic malignancy. A full-thickness segment from the anterior aspect of the body of the gallbladder was removed and placed in cold Kreb's solution in an organ bath. Concentration–response curves were obtained for BK $0\cdot1$–$100\,\mu$mol l^{-1} and repeated in the presence of selective B1- and B2-receptor antagonists. A response to a fixed concentration of BK 10 μmol l^{-1} was determined in the presence of variable amounts of each antagonist.

Results Fourteen viable strips were obtained from five normal gallbladders and 26 viable strips from 12 diseased gallbladders. Both groups showed a similar and repeatable concentration–response curve to BK (mean(s.e.m.) ED_{50} 4·9(5·7) and 5·1(7·3) μmol l^{-1} respectively). B1-receptor blockade produced a marked rightward shift of the curve in normal but not diseased strips (ED_{50} 26·6 and 8·5 μmol l^{-1}). When the concentration of des-Arg^9-Leu^8 was increased no difference in the level of inhibition was noted. B2-receptor blockade produced a marked rightward shift in both normal and diseased gallbladder strips (ED_{50} 37·1 and 27·5 μmol l^{-1}). At high concentrations of BK the response was not affected by the presence of the antagonists.

Conclusion Human gallbladder strips contract to BK in a dose-dependent manner. At low concentrations, BK produces contractions in normal gallbladders via B1 and B2 receptors but only via B2 receptors in diseased gallbladders. At high concentrations, BK acts via another BK receptor or a by a receptor-independent mechanism.

Serum cholecystokinin levels in normal individuals, patients with gallstones and individuals with irritable bowel syndrome

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Background Cholecystokinin (CCK) is widely distributed throughout the gastrointestinal tract. It stimulates gallbladder contractions and intestinal motility. Factors that control the release of CCK include neural and hormonal mechanisms and intestinal luminal factors. This study aimed to determine the relationship between gallbladder contraction and CCK release in patients with gallstone disease, healthy individuals and in individuals with irritable bowel syndrome (IBS).

Methods Blood (6 ml) was taken from fasting individuals and then again at 15, 30, 45 and 60 min after ingestion of a standard fatty meal. Ultrasonographic measurement of gallbladder volume was performed at 5-min intervals. CCK was extracted from each blood sample and a radioimmunoassay was performed.

Results Forty-six individuals were studied, 24 with gallstones, nine who had IBS and 13 controls. The patients with gallstones were divided on the basis of the ultrasonographic findings: good contractors ($n = 6$) with an increase in gallbladder volume of more than 50 per cent after a meal and poor contractors ($n = 18$). Patients with gallstones and a poorly contracting gallbladder had higher CCK levels (mean(s.e.m.) 4·35 (0·44) pmol l^{-1}) than healthy individuals (3·37(0·25) pmol l^{-1}). No significant difference was noted in serum CCK levels between normal individuals and good contractors with gallstones. Patients with IBS had higher mean levels of CCK while fasting (2·23 (0·25) pmol l^{-1}) than normal individuals (1·10(0·26) pmol l^{-1}) and patients with gallstones (1·40(0·17) pmol l^{-1}). Patients with IBS also had higher peak levels of CCK (7·83(0·56) pmol l^{-1}) than both patients with gallstones (4·34(0·25) pmol l^{-1}; $P < 0·1$, *t* test) and healthy individuals (3·37(0·25) pmol l^{-1}; $P < 0·05$). The peak ejection fraction was higher in patients with IBS (mean(s.e.m.) 72(10) per cent) than normal subjects (62(5) per cent) or those with gallstones (30(8) per cent).

Conclusion Raised levels of CCK release in patients with a poorly contracting gallbladder may be due to impaired negative feedback. High levels of CCK and higher ejection fractions in IBS raise the possibility of a contribution by this hormone to the generalized increase in gastrointestinal muscle tone.

Determinants of outcome for cimino fistulas used for rapid high-flux haemodialysis

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Background The influence of patient-related variables on the outcome of radiocephalic (cimino) fistulas, used as primary access for rapid high-flux haemodialysis, was assessed.

Methods Over 3 years 107 patients had cimino fistulas created. Operations were performed or supervised by a single surgeon. Prosthetic, other autogenous and repeat fistulas were excluded. Patient variables, including age, sex, cause of renal failure, hypertension, heart disease, peripheral vascular disease, diabetes, smoking, aspirin, erythropoeitin, warfarin, haemoglobin, plasma albumin and local factors (previous subclavian or internal jugular dialysis catheter, early dialysis flow rates) were collected prospectively. Patients were followed up (median 24 months) until access failure, transplantation or death. Univariate, multiple logistic regression and life-table analysis were used to assess factors determining cimino patency.

Results Primary patency was 69 per cent at 12 months and 56 per cent at 24 months. By univariate and multivariate analysis, cimino failure was more common in patients with diabetes ($P = 0·009$ and $P = 0·03$), females ($P = 0·04$ and $P = 0·02$) and young patients ($P = 0·02$ and $P = 0·02$). The mean(s.d.) fistula flow rates averaged over 1 month were 379(78), 392(74) and 375(78) ml min^{-1} at 6, 12 and 24 months respectively (dialysis efficiency 95–100 per cent). Mean(s.d.) flow rates at 3 months were significantly lower for the 17 fistulas that occluded between 6 and 24 months (343(82) ml min^{-1}) than the 46 fistulas that remained patent throughout this period (393(74) ml min^{-1}) ($P = 0·03$). Other factors did not predict outcome. Results of actuarial analysis are presented in the *Table*.

Conclusion Cimino failure is more likely in female and diabetic patients. Consideration should be given to alternative forms of dialysis access in these patients. Failure is predicted by reduced early flow rate.

Early endothelin 1 rise predicts renal failure following supracoeliac clamping

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Background Early acute renal failure (ARF) following aneurysm repair is associated with a high mortality rate. Endothelin (ET) 1 is a potent vasoconstricting peptide, and endothelial ischaemia and reperfusion are thought to stimulate its release. It causes reduced renal microcirculatory flow and glomerular filtration rates in animal models, but there are few reports of raised

	Patency at 24 months (%)					
	Above median age ($n = 53$)	Below median age ($n = 53$)	Male ($n = 73$)	Female ($n = 34$)	Non-diabetic ($n = 77$)	Diabetic ($n = 30$)
Primary	59	41	62	24*	61	35†
Secondary	65	61	74	44*	70	49†

*$P < 0·05$ *versus* male, †$P < 0·05$ *versus* non-diabetic (log rank test)

assessing change following both surgical and non-surgical intervention in PVD.

Long-term outcome of stenting in long iliac artery lesions

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Background A cohort study was undertaken at 12 months to assess the long-term outcome of aortoiliac stenting of lesions larger than 5 cm. A total of 34 consecutive patients were identified from the radiology files and recalled for assessment by duplex, ankle:brachial pressure index (APBI) and clinical grading using the Fontaine score (I, asymptomatic; IIA, mild claudication; IIB, severe claudication; III, rest pain; IV, tissue loss). Thirty-one patients were assessed (three failed to attend); six patients had bilateral stents.

Methods There were 27 men and seven women, of median age 63 (range 43–83) years. Nine patients presented with mild claudication, 17 with severe claudication, five with rest pain and three with tissue loss. Median ABPI before treatment was 0·5 (range 0–0·9). There were 30 occlusions and ten stenoses. The median lesion length was 7 (range 5–10) cm; 22 lesions involved the common iliac artery only, 11 the external iliac and seven involved both vessels.

Results One patient developed an acute thrombosis at 3 weeks which was successfully treated by thrombectomy. Three patients subsequently required additional procedures for continuing ischaemia at a different anatomical site (one femoral and one popliteal angioplasty; one femoropopliteal graft). At 12-month assessment Fontaine score showed that 27 patients were asymptomatic, five had mild claudication and two had severe claudication. Median ABPI was 0·9 (range 0·4–1·3); the median improvement in ABPI was 0·4 (range 0–1·0). Duplex ultrasonography identified seven cases of stent restenosis. Duplex examination at 1 year determined that the primary patency rate for aortoiliac stenting was 82 per cent (Kaplan–Meier analysis). A high risk of stent restenosis was associated with smoking ($P<0·05$) and hyperlipidaemia ($P<0·05$) (χ^2 test with Bonferroni's correction).

Conclusion Stent restenosis in patients with long iliac artery lesions (greater than 5 cm) is a significant problem, indicating the need for a regular duplex surveillance programme.

Ruptured abdominal aortic aneurysm: morphology and outcome

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Background Ruptured abdominal aortic aneurysm (AAA) occurs at the point where wall stress overcomes the tensile strength of the aortic tissue. Characteristics of the patient and aneurysm may influence this balance. The aim of this study was to relate the morphology of the ruptured AAA to the clinical characteristics and outcome of the patient.

Methods Over a 5-year period 46 patients with ruptured AAA (11 identified at operation and 36 at autopsy) were examined to assess the number and site of aneurysm rupture, the characteristics of the aneurysm (site, shape, length, diameter and associated iliac aneurysm) and the presence and site of retroperitoneal or intraperitoneal haematoma. The patients were also assessed for the following associated conditions: ischaemic heart disease (IHD), hypertension, renal impairment, diabetes, cerebrovascular disease, carcinoma and chronic lung disease (COAD). Patients undergoing successful operations were followed until death. Univariate and stepwise multiple regression analyses were used to identify variables predicting the site of aneurysm rupture and survival.

Results A range of aneurysm sizes (median diameter 9 (range 5–14) cm; median length 11 (range 8–18) cm) and types (40 infrarenal, four juxtarenal and two suprarenal) were found. Most ruptures (73 per cent) occurred in the middle third of the aneurysm. In the transverse dimension ruptures were distributed around the circumference of the aneurysm but few ruptures (four) were in the left posterior quadrant. The site of rupture in the transverse dimension predicted the position of the retroperitoneal haematoma ($P=0·0001$). By univariate and multiple regression analysis, the only variable that significantly predicted the quadrant of rupture was the presence of COAD ($P=0·04$ and $P=0·01$). All six patients with COAD suffered ruptures on the right side from 7 to 10 o'clock. A history of carcinoma ($P=0·007$), aneurysm shape ($P=0·03$) and COAD ($P=0·04$) predicted the level of rupture. Nine of the 46 patients underwent successful operations and survived for a median of 4 (range 3–10) years. Most patients (31) died before reaching hospital or could not be resuscitated. The most significant factor predicting outcome was the transverse site of aneurysm rupture ($P=0·0004$ and $P=0·004$): all four patients in whom the rupture was in the left posterior quadrant survived compared with only one of the 14 who had a right posterior rupture. Survival was also predicted by the absence of IHD ($P=0·02$ and $P=0·02$) and iliac aneurysm ($P=0·05$ and $P=0·02$).

Conclusion These data suggest that the site of aneurysm rupture, which may be in part predicted by the clinical characteristics of the patient, influences outcome.

Change in abdominal aortic aneurysm diameter following stenting

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Background If aortic stent grafts are to succeed in the treatment of abdominal aortic aneurysm (AAA), they must exclude the aneurysm sac from the arterial circulation. Failure to do this may result in a continued increase in AAA size and continued risk of rupture. Early changes in AAA diameter following radiologically successful aortic stenting were examined.

Methods Forty-seven AAAs were repaired using a bifurcate system. The maximum aortic diameter was recorded for each patient on a preoperative computed tomography (CT) scan. Regular follow-up scans were examined for endoleak and change in AAA diameter by a consultant interventional radiologist. Patients were grouped according to initial AAA size (group 1, 45–54 mm; group 2, 55–64 mm; group 3, greater than 65 mm).

Results Forty-two patients reached 1-month follow-up (range 1–26 (median 11) months).

	Group 1	Group 2	Group 3
No. of patients	12	11	5
Median follow-up (months)	6	4	2
Median (range) diameter change (mm)	−4·3 (−12·5 to +4·4)	−2·8 (−40·4 to +9·4)	−3·6 (−28·8 to +7·4)

Twenty-seven AAAs decreased in size, one despite a small persisting endoleak. In 15 patients, the aneurysm sac either remained the same (six patients) or increased in diameter (nine).

In only one of these did CT detected an endoleak, which closed spontaneously at 3 months.

Conclusion Despite a median diameter decrease in all groups, CT revealed shrinkage of the sac in only 27 of 42 patients. AAA diameter was actually increasing in nine patients, despite an apparently successful procedure. These early findings are worrying and may reflect inadequate exclusion of the AAA from the systemic circulation.

Epidemiology of abdominal aortic aneurysm in the Asian population

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Background The incidence of abdominal aortic aneurysm (AAA) per 100 000 in the UK has been reported as 11·3 for men and 3·0 for women. However, there are few studies relating to the ethnic origin of AAAs and none relating to the Asian population. The incidence of AAA in the population of Bradford was examined and any difference in incidence between the Asian and Caucasian population was sought.

Methods A retrospective study over the period 1989–1997 was performed. Population statistics were acquired from census records at Bradford City Council. The number of aneurysms was determined from the Patient Administration Service, consultant-held databases and theatre records. Details of all aneurysms presenting over the study period were obtained from the case notes.

Results There were 233 AAAs in patients aged 55–90 years (incidence 29 per year). The expected number was 33 per year ($P > 0{\cdot}05$, χ^2 test). The Asian community make up 13·6 per cent of the total population. There were no AAAs recorded among Asians, although the expected incidence was five per year, i.e. 40 Asian aneurysms over the period of the study ($P < 0{\cdot}05$, χ^2 test).

Conclusion The overall observed incidence of AAA was similar to the expected incidence. However, there was a significant difference between the observed and expected number of aneurysms in Asians. Despite the high incidence of peripheral vascular disease in this group there were no cases of AAA.

Factors influencing intrasac pressure following endovascular aortic aneurysm repair

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Background It is generally assumed that following successful endovascular aortic aneurysm repair (EVAR) the excluded sac becomes depressurized and subsequently thromboses. In a preliminary clinical study intrasac pressure measurements were made for up to 36 h after operation in a series of 11 patients undergoing EVAR. In successful cases (ten of 11) mean intrasac pressure (MIP) remained the same as mean systemic pressure (MSP) but was associated with a significant fall in the pulse pressure ($P < 0{\cdot}01$ for all time periods; Mann–Whitney U test). In one patient with a proximal endoleak there were no recordable differences between intrasac and systemic pressure. An *in vitro* model was constructed in order to examine factors influencing intrasac pressure following EVAR.

Methods Studies were performed with a simulated aneurysm model perfused with a saline–glycerol mix under physiological flow conditions. Perfusion of the sac by a side branch was simulated by connecting a sac outlet to the 'aorta' upstream. Pressure measurements were made following deployment of a commercial stent-graft system and then with the device gelatin coated to eliminate perigraft leakage. Measurements were made with the side branch patent and occluded.

Results After deployment of the standard device MIP fell by a mean of 38 mmHg compared with MSP. Side-branch patency had no effect on MIP while some perigraft leakage was evident. Following complete sac occlusion with the coated graft, however, MIP remained the same as MSP (thus mimicking the clinical study) with the side branch patent, but fell to negligible levels when it was occluded ($P < 0{\cdot}01$, paired t test).

Conclusion These findings suggest that following successful EVAR, with the sac excluded from aortic flow, intrasac pressure is generated by side-branch perfusion, i.e. via patent lumbar and/or inferior mesenteric arteries. Thrombosis of these vessels appears to be required for the sac to become depressurized but this was not observed in the clinical study within the first 36 h. Further work is required to determine the time scale of these events and also to assess the significance of patent side branches demonstrated before operation, as embolization may be required to guarantee a successful procedure in the long term.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Malone antegrade continence enema for faecal incontinence and constipation in adults

Sir

I read with interest the original paper by Krogh and Laurberg (*Br J Surg* 1998; 85: 974–7). Their encouraging results with this simple method of drug administration directly to the proximal colon prompted the thought of other possible uses for this technique. For instance, could an appendix stoma be used in the delivery of steroids to the colon in patients with ulcerative colitis? A suitable steroid injection would move antegradely down the large bowel and might come into contact with greater lengths of colon than could be achieved by any enema. I wonder whether the potential for this operation has not yet been fully realized?

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Role of arteriography in the selection of patients for carotid endarterectomy

Sir

We read with interest the paper by Bain *et al.* (*Br J Surg* 1998; 85: 768–70) in which they concluded that endarterectomy cannot be performed safely without routine angiography because it is unable to detail the anatomy or determine the extent of carotid disease and may lead to inappropriate decision-making. These are fairly sweeping conclusions given that the comparative study was made between duplex ultrasonography and uniplaner conventional contrast angiography.

This paper is based on the premise that contrast angiography is the gold standard. The authors appear to have concluded that if a severe stenosis was detected on duplex imaging with no evidence on a uniplaner conventional angiogram, then the imaging was wrong. We would suggest that the converse was true and that if the authors had performed biplaner views it would have confirmed the duplex findings. This potential discrepancy is also corroborated by the fact that the authors made a further analysis after exclusion of patients whose arteriograms were subject to observer error, i.e. accuracy in stenosis measurement could not be achieved. As this amounted to some 58 patients, this has the potential to confound meaningful interpretation of the study.

We are told that arteriography provided additional information in 89 patients. We would dispute that duplex ultrasonography cannot interpret the relative positions of anatomical structures such as the internal carotid artery and the mandible. We do not understand how the diagnosis of a high carotid bifurcation can only be achieved by angiography. In our experience of over 500 consecutive carotid endarterectomies with only 15 patients undergoing preoperative carotid angiography, duplex ultrasonography is more than capable of diagnosing and localizing high carotid bifurcations and diagnosing the small number whose upper limit of disease is outwith the scanning range of the machine.

Angiography has two main advantages: it can diagnose siphon disease and, very rarely, there are patients in whom there is discrepancy between subtotal occlusion and internal carotid artery occlusion. As a general rule, however, there is no clinical evidence that tandem disease (carotid artery and siphon) increases operative or long-term risk, and with the newer state-of-the-art duplex machines, it has been our experience that they are far more sensitive at picking up a very small residual channel than angiography. Finally, the authors comment that in 26 patients surgery was not performed because of information obtained from the angiogram. Having scrutinized the paper, we could not identify the 26 patients in whom surgery was not performed and perhaps the authors would provide this information as this is certainly an important observation.

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Author's reply

Sir

Arteriography was the basis of patient selection in both the European and North American Clinical Trials. Proponents of biplanar arteriography have not reported the size of the difference between different views, or derived an agreed adjustment when there is disagreement between percentage stenosis on different views.

Duplex ultrasonography was undertaken by an experienced ultrasonographer using a linear array 5-MHz probe (type L538) and an Acuson (Acuson, Uxbridge, UK) 128 duplex scanner. Regular quality analysis of the duplex ultrasonography is presented and shows an acceptable accuracy of definition of stenosis. The criteria used by the ultrasonographer for grading a stenosis 'high' was based on access at the angle of the mandible and took account of the patient's habitus. Twenty-six patients did not have surgery following arteriography for the following reasons: less than 50 per cent stenosis (seven); extensive atheroma (six); high stenosis (four); narrow internal carotid (three); siphon disease (one); tortuous internal carotid (one); internal carotid occlusion (four).

The surgical premise was to identify and exclude from surgery patients with a high stenosis, extensive atheroma or a narrow internal carotid in whom surgical difficulties would be anticipated. Thirteen of the 272 patients were excluded for this reason. This premise is borne out in the recent meta-analysis that identified a high stenosis as one of the seven factors correlating with an increased risk of surgical stroke[1]. In the series reported in this paper, duplex ultrasonography identified only three of these 13 patients.

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1 Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review. *BMJ* 1997; 315: 1571–7.

Continuous antibiotic treatment for experimental abdominal sepsis: effects on organ inflammatory cytokine expression and neutrophil sequestration

Sir

I read with interest the article by Mercer-Jones *et al.* (*Br J Surg* 1998; 85: 385–9) which demonstrated the possibility of investigating local tissue cytokines in an experimental model of abdominal sepsis. We feel the authors failed to use the appropriate statistical methods and made the wrong conclusions.

The data were presented in the form of median values and interquartile range. At the same time, Student's *t* test was used to compare serum endotoxin and pulmonary myeloperoxidase levels even though this is a parametric test and no mention was made of the normal distribution assumptions.

The authors compared log colony forming units per ml between the intermittent and continuous cefoxitin and saline control groups in *Table 2* and concluded from this that continuous infusion of cefoxitin significantly reduced blood cultures compared with intermittent cefoxitin dosing without comparing the continuous and intermittent groups.

In *Table 2* median value of serum endotoxin in the continuous cefoxitin group is outside the interquartile range, this is mathematically impossible.

The authors used the word 'correlation' to describe their data several times without mentioning a single correlation coefficient value. From a statistical point of view, it is possible to measure the correlation coefficient by carrying out regression analysis on their data.

Two of the references[1,2] quoted in support of the effectiveness of continuous *versus* intermittent antibiotic dosing in animal studies are not appropriate as these studies demonstrated effectiveness of continuous antibiotics in immunosuppressed animals where there is a relative depletion of white cells and cytokines.

Finally, the authors' conclusions can only be derived after performing linear regression and correlation coefficients using bacteraemia scores and local tissue cytokine levels as a predictor and an outcome respectively.

Therefore, further animal studies looking at morbidity and mortality as endpoints are required as the clinical significance of raised cytokine level has not been proven to be directly related to patient outcome.

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1 Livingston DH, Wang MT. Continuous infusion of cefazolin is superior to intermittent dosing in decreasing infection after hemorrhagic shock. *Am J Surg* 1993; 165: 203–7.
2 Roosendaal R, Bakker-Woudenberg JA, van den Berghe-van Raffe M, Vink-van den Berg JC, Michel BM. Impact of the dosage schedule on the efficacy of ceftazidime, gentamicin and ciprofloxacin in *Klebsiella pneumoniae* pneumonia and septicemia in leukopenic rats. *Eur J Clin Microbiol Infect Dis* 1989; 8: 878–87.

Author's reply

Sir

We appreciate the detailed interest that Messrs Mokbel and Saunders had in our work. For all data (both parametric and non-parametric) the underlying statistical test assumptions were upheld. The error that we made was in incorrectly stating which tests were performed. Multiple comparisons require either analysis of variance for parametric data and not Student's *t* test) or Kruskal–Wallis (for non-parametric data rather than Mann–Whitney *U* test) which were used to analyse these data[1]. The statistical significances for the blood cultures are correct as described in the legend for *Table 2*, but the description in results was inadequate. Multiple comparison analysis of the three groups showed that only continuous infusion of cefoxitin significantly reduced blood cultures compared with saline controls.

There were no significant differences when the intermittent group was compared with other groups. We apologize for this oversight. The correct high confidence limit for serum endotoxin in *Table 2* for continuous cefoxitin should be 3·7 instead of 2·7. We agree that, because we did not present correlation coefficients (which we have done in previous work), the term 'association' should have been used.

We do believe that the references used to support continuous antibiotics were appropriate. They were meant to show the paucity of research into the effect of antibiotic usage in non-immunosuppressed models as pointed out in the introduction. Linear regression analysis was not attempted because of the non-parametric nature of much of the data and the inability to prove homoscedasticity[1]. We agree that serum cytokine levels (except interleukin (IL) 6) have not correlated with clinical outcome in patients with sepsis. The aim of this paper was to show that bacteraemia, rather than endotoxaemia, was associated with tissue proinflammatory (tumour necrosis factor, IL-1) cytokine messenger RNA levels and potentially injurious neutrophil sequestration. We believe the data show that continuous antibiotic administration may be more efficacious in this regard, but certainly agree that more research is required to clarify these issues.

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1 Zar JH. *Biostatistical Analysis*. 2nd ed. New Jersey: Prentice-Hall, 1984.
2 Hadjiminas DJ, McMasters KM, Peyton JC, Cook MD, Cheadle WG. Passive immunization against tumor necrosis factor and interleukin-1 fails to reduce lung PMN sequestration in chronic sepsis. *Shock* 1994; 2: 376–80.

British Journal of Surgery 1998, 85, 1596–1597

Book reviews

Pancreatitis

P. G. Lankisch and P. A. Banks (eds). 240 × 160 mm. Pp. 377. Illustrated. 1998. Berlin: Springer. £57.

This book is an excellent review of all relevant topical thinking about both acute and chronic pancreatitis. The two authors, one from Germany and one from the USA, have combined to cover the fields comprehensively. This will be an invaluable reference source for anybody with an established interest in pancreatitis or involving themselves with it for the first time. Clear guidelines are produced for the management of problems and the authors present different points of view, yet steer a sensible course advocating sensible treatment options. I have only a few minor quibbles. This is autumn 1998 yet the preface written by the authors is dated summer 1997. The bibliography is very impressive but already out of date. There is also a surprising number of typographical errors including a significant one on the first page of the preface.

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Understanding Surgical Disease. The Miami Manual of Surgery

M. G. McKenney, P. C. Mangonon and J. A. Moylan (eds). 278 × 215 mm. Pp. 445. Illustrated. 1998. Philadelphia, Pennsylvania: Lippincott-Raven. US $63.

This book was written for medical students to give enough surgical education for them to pursue non-surgical careers. It is written for an American audience with each chapter prepared by a surgical faculty member of less than 10 years standing and a senior faculty member. This balance is supposed to combine the wisdom of age and experience with the practical needs of everyday management. The book appears too detailed for UK medical students, yet not detailed enough for those preparing for higher surgical examinations. My senior house officers found it useful to dip into between cases and the overall view was that this was a book for the theatre coffee room rather than serious study. As expected, the thrust is American which makes it slightly less relevant to UK practice.

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Modern Surgical Care. Physiologic Foundations and Clinical Applications. 2nd ed.

T. A. Miller (ed.). 285 × 220 mm. Pp. 1454. Illustrated. 1998. St Louis, Missouri: Quality Medical Publishing. DM 295.

This is a very welcome second edition of an excellent textbook, the first edition of which was produced in 1988 and immediately well received. The original title was *Physiological Basis of Modern Surgical Care* and the new title is helpful in its indication of the very applied nature of the work to clinical practice. The whole emphasis, as with the first edition, is on the way in which derangement of physiology brings about surgical disease and explains many of the signs and symptoms, and correlates with changes in laboratory, radiological and scanning investigations. To this end, each chapter has been revised and some omitted. The total number of contributors, almost all from the USA, is 138, of whom 80 are new to this edition. The emphasis is on general surgery and so work on reproductive organs, the musculoskeletal system and head and neck (other than thyroid and parathyroid glands) has been omitted.

The book has accomplished its aim superbly. The work is scholarly, well written and very up to date. The rapidly changing areas concerning such entities as peptic ulceration, gastrointestinal haemorrhage, inflammatory disorders of the small bowel and colon, transplantation and cerebrovascular disease are particularly well covered. The bibliography is extensive and contemporary with many original papers being quoted from within the past 2 years. This book should be read by or be available for reference to all general surgeons, particularly trainees and new consultants.

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Surgical Research. Basic Principles and Clinical Practice. 3rd ed.

H. Troidl, M. F. McKneally, D. S. Mulder, A. S. Wechsler, B. McPeek and W. O. Spitzer (eds). 259 × 180 mm. Pp. 695. Illustrated. 1998. New York: Springer. £68·50.

When I was first asked to review this book it sat on my desk staring at me for a number of days. From a distance it did not look very impressive but did look rather daunting because of the number of pages. Having finished going through it, however, I soon came to ask myself: Where has it been all my career? I am ashamed to say this book was new to me, although it is now in its third edition. I have also to admit that with 671 pages of text I have not read it cover to cover. However, I have read enough of it to realize that it should be in the library of every academic surgical unit throughout the world. Indeed, I would go so far as to say that any surgeon contemplating a career in academic surgery should own a copy of this text.

Over 100 individuals have contributed to this volume which is edited by six individuals with a clear track record in academic surgery. Although five of the editors are based in North America, the list of contributors is truly international, coming from North America, Europe, Asia and the Far East. The book is extraordinarily comprehensive in its approach to surgical research, starting with a wonderful section on the history of research. The chapter on historical perspectives and that dealing with surgeons who have won the Nobel Prize are both compelling reading that should be inspirational for anybody in this field. At the opposite end of the book, the chapter on future prospects in surgical research by Francis Moore represents the other end of the spectrum. In between is a comprehensive step-by-step guide to organizing an academic career. This book is, of course, highly topical in the present day; while the editors have attempted to adapt to the rapidly changing field of surgical research, many of the sections have a timeless quality. The entire section on reading, writing and assessing manuscripts will stand for many years and the advice offered to potential fund-raisers is also well worth reading. I strongly recommend that this book be purchased by anybody pursuing a career in academic surgery; such an individual would do well to dip a toe into this manuscript on a regular basis.

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Injury in the Young

M. P. Ward Platt and R. A. Little (eds). 253 × 172 mm. Pp. 317. Illustrated. 1998. Cambridge: Cambridge University Press. £55.

This book is a compilation of disparate topics, ranging from a philosophical discussion of children's autonomy and rights through detailed description of neuroembryology to lucid explanation of the pathophysiological consequences of near drowning, submersion and immersion. The biochemical, metabolic and immunological responses to various forms of trauma are well described with minimal repetition for a multiauthor text. Similarly, demographic data and important issues such as nutritional requirements and support are clearly itemized. There is almost something of interest and value for any clinician involved in the reception, resuscitation or ongoing management of the injured child. However, there are contributions which must constitute obligate reading for this group, and child death in the accident and emergency department is such an example of practical and informative writing that is not otherwise easily accessible to a surgical readership. The editorial preface, which indicates a target readership of both clinician and researcher, fails to stimulate or do justice to what is a varied but well written and apposite contribution to the literature. A casual glance at the chapter list may prejudice a surgeon against purchase. Indeed, but for the invitation to review this book it might not have been on my reading list; that would have constituted a serious error of judgement on my part. This book is relevant and contemporary (although no reference is more recent that 1995) and is not an acquisition for the departmental library. It is a text to be read by trainee and trainer, surgeon, anaesthetist, emergency room doctor and paediatrician, and to be read now.

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Extraperitoneal Laparoscopic Surgery

C. G. Eden (ed.). 283 × 222 mm. Pp. 157. Illustrated. 1997. Oxford: Blackwell Science. £69·50.

The title of this book promises much, but it unfortunately fails to deliver on its potential. With John Wickham's lead the urological surgeons have for long employed a percutaneous extraperitoneal approach to the renal tract. The increasing use of the laparoscope in general surgery has led to major changes in practice and also complications due to a, perhaps unnecessary, transperitoneal approach. An instructional text on extraperitoneal laparoscopy drawing together the disciplines of general surgery and urology is thus welcome. The general layout of the chapters allows for unnecessary repetition and confusion. Anaesthesia comes after access and should do more to discuss the complications of the extraperitoneal technique. Access is mentioned, with photographs in the introduction, and then has a chapter of its own. The latter is more an advertisement for the Guar balloon than a genuine discussion of the different approaches to the retroperitoneum. To confuse or annoy the reader further, most authors not only describe port-site application, which is entirely reasonable, but also include a section of their own on how they personally gain access. This takes up a lot of space, is repetitive, and can be confusing. A chapter on extraperitoneal laparoscopic operating in the pig seems inappropriate. There is a further chapter on tissue approximation, which reads as though it has been lifted and inserted because the editor wrote a thesis rather than adding anything useful to the book. The line diagrams are generally well drawn, but the operative photographs are often out of focus and of poor quality. This is not an operative text from which one could perform a procedure unaided, nor does it generally inspire. Perhaps it will appeal to urological surgeons, but it is of little or no value to the general surgical community.

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Atlas of Urologic Surgery. 2nd ed.

F. Hinman Jr (ed.). 308 × 235 mm. Pp. 1172. Illustrated. 1998. Philadelphia, Pennsylvania: WB Saunders. Price not supplied.

As the title suggests, this book is an extremely useful and practical guide to urological operations. As such it will be of special interest to specialist registrars and consultants who wish to consolidate their initial experience in subspecialist areas of operative urology. The operative descriptions are excellent and the illustrated steps are some of the very best. The standard of illustrations is excellent; this is one of the best operative textbooks available. All subspecialist areas of urology are considered and the contributory commentators are all well respected in their fields, including authors from both Europe and the USA. At the end of each operative description commentaries are given that are clear and concise. These are, of necessity, sometimes biased and, although they are given by world experts in their field, the reader must be prepared to challenge some of the surgical dogma that is expressed. However, these commentaries are good and provocative, their only deficiency being that they are not in any way comprehensive with regard to clinical management of the conditions in question.

Interestingly, the commentaries are sometimes at variance, or in disagreement with, the operative text, sometimes suggesting improvements on the foregoing classical descriptions of a given operation. One deficient area in the book is the section on reconstructive urology and, in particular, orthotopic neobladder substitution. This section is a little short which may be a drawback as it tends to be an area of great interest to modern reconstructive urologists. This is an area which is changing rapidly, however, and brevity may be appropriate. In summary, while this is a superb operative manual with clear and concise illustrated operative descriptions, it should not be taken as comprehensive with regard to clinical management of the conditions described.

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Scientific Surgery

The British Journal of Surgery is committed to practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English language publications. The full list of all these papers will be available in the Scientific Surgery Archive which will be held on *The British Journal of Surgery* website together with links to free Medline sites where abstracts can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Randomized trials

Dahlberg M, Glimelius B, Graf W, Pahlman L. Preoperative irradiation affects the functional results after surgery for rectal cancer: results from a randomized study.
Dis Colon Rectum 1998; 41: 543–9.
More results from the Swedish Rectal Cancer Study: 203 patients alive after 5 years answered a questionnaire. Patients who had radiotherapy had an increased incidence of incontinence to loose stools, urgency and emptying difficulty, though sensory function was similar in both groups

Kale TI, Kuzu MA, Tekeli A, Tanik A, Aksoy M, Cete M. Aggressive bowel preparation does not enhance bacterial translocation provided the mucosal barrier is not disrupted: a prospective, randomised study.
Dis Colon Rectum 1998; 41: 630–41.
Three different bowel preparations and a control group including a total of 82 patients were studied. Bacterial translocation was rarely identified suggesting it is not enhanced by bowel preparation.

Rougier P, Sahmoud T, Nitti D, Curran D, Doci R, De Waele B *et al.* Adjuvant portal vein infusion of fluorouracil and heparin in colorectal cancer: a randomised trial.
Lancet 1998; 351: 1677–81.
A total of 1235 patients were included. Five year survival rates were similar 72 *versus* 73 per cent in controls. This regimen cannot be recommended as sole adjuvant therapy in colorectal cancer.

Ho Y-H, Lee J, Salleh I, Leong A, Eu KW, Seow-Choen F. Randomized controlled trial comparing same-day discharge with hospital stay following haemorrhoidectomy.
Aust N Z J Surg 1998; 68: 334–6.
Fifty-four consecutive patients were randomized; 'stay' patients remained in hospital until after a bowel movement (median 2 days) There were no differences in complication rates, pain scores and recovery times but patients preferred to stay in hospital after surgery.

Squirrel DM, Majeed AW, Troy G, Peacock JE, Nicholl JP, Johnson AG. A randomised, prospective, blinded comparison of postoperative pain, metabolic response, perceived health after laparoscopic and small incision cholecystectomy.
Surgery 1998; 123: 485–95.
In this study of 200 operations, laparoscopic surgery had a reduced systemic inflammatory response and caused less postoperative pain. However, recovery rates and perceived health measurements were similar

Sanders CJ, Battistella FD, Whetzel TP, Stokes RB. Percutaneous diagnostic peritoneal lavage using a Veress needle *versus* an open technique: a prospective randomized trial.
J Trauma 1998; 44: 883–8.
Some 176 patients who needed peritoneal lavage following blunt trauma were included. The open method took longer but had fewer technical failures (4 *versus* 11 per cent). Both were safe, there was only one complication, a wound infection.

Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials.
Lancet 1998; 351: 1451–67.
Fifty-five trials were included. For patients with oestrogen receptor positive or unknown tumours, the survival advantage was unequivocal. Oestrogen receptor negative tumours require further study.

Morrell CJ, Walters SJ, Dixon S, Collins KA, Brereton LML, Peters J *et al.* Cost effectiveness of community leg ulcer clinics: randomised controlled trial.
BMJ 1998; 316: 1487–91.
A total of 233 patients with venous ulcers were included. Ulcers treated in the community clinics by four-layer bandaging were more likely to be healed after 12 weeks (34 *versus* 24 per cent for controls).

Golub R, Siddiqui F, Pohl D. Laparoscopic *versus* open appendectomy: a meta-analysis.
J Am Coll Surg 1998; 186: 545–53.
Sixteen randomized trials were evaluated. Laparoscopic surgery reduces the incidence of wound infection and speeds recovery. A trend towards a higher rate of intra-abdominal abscess needs further study.

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Preparation of manuscripts

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Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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Correspondence

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Abstract

This should be not more than 200 words on the second page of the manuscript and be presented in a structured format. **Background:** state why the study was done, and its main aim; **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings of the study; include important numerical values. **Conclusion:** state the main conclusion drawn from the results. Controversial or unexpected observations may be highlighted, but keep this section brief. Write the abstract in clear prose.

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Use abbreviations sparingly. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension by the reader. Use abbreviations consistently throughout the text and clearly define each one on first use.

Numbers and units

Use the decimal point, not a comma, e.g. 5·7. Use a space and not a comma after thousands and multiples thereof, e.g. 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, give the actual values and units, with SI equivalents inserted in parentheses at appropriate points.

Statistics

For detailed guidance on the handling of statistical material, consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; **276**: 637–9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Do not use the '±' symbol; these statistics should be presented in parentheses after the mean value.

Analysis

Clearly describe which methods were used for which analyses; any methods not in common usage should be supported by references. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value, e.g. '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$'.

Actual *P* values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Do not confuse statistical significance with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

References

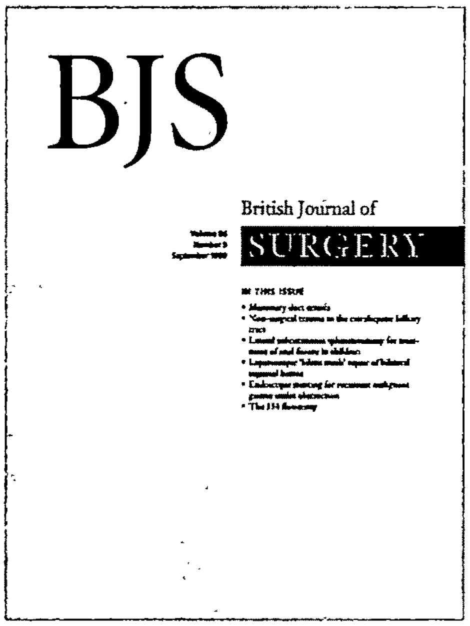
Type the references with double spacing in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged. Reference to unpublished communications will not be accepted. Cite personal communications in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, number the references consecutively by superscript: [1] or [1-3]. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer, 1981: 123–63.

British Journal of Surgery 1998, 85, 1601–1602

Leading articles

A new British Journal of Surgery



BJS

British Journal of

SURGERY

The January 1999 issue will strike you immediately as different. Not only will a new cover grace the Journal's front, but layout and content will also be different.

Content

Readership surveys have been a valued means of advising policy and style. Recent responses have described an 'intense', 'full' and 'reader-unfriendly' journal. In the past 2 years the editors have initiated 'away days' to allow publishers, editors and invited external critics to examine all aspects of the Journal outside the more formal environment of the Editorial Board and Council. These two mechanisms have led to the new format and content which have the full support of the Editorial Board and Council.

The same number of pages will be retained but with a more relaxed layout of articles – wider margins and better spacing of abstracts, text, illustrations and tables. In addition, editors, publishers and typesetters will work toward a unification of illustration style. Colour will still be encouraged. Tables will have a new highlight.

Slightly fewer articles will be published in each issue. Readership advice and editorial policy has moved away from short articles and toward the encouragement of full-length clinical and scientific pieces. Case reports and surgical workshops will only rarely be accepted. Leading articles and Reviews will continue but two new types of article will emerge. The first will describe strategy for difficult clinical or operative situations and the second will be commentaries on conflicting, innovative or controversial papers. Time to publication will probably remain at about the current 5 months. It has been 6 or 7 months for the past 2 years. Some of this improvement is gratefully attributed to the international panel of referees who continue to support the Journal unstintingly with high-quality, objective reviews returned in a timely fashion.

The referee process

A previous study by the Journal published results showing concordance between referees and demonstrated how referee opinion influenced the acceptance/

rejection process. A second study led by Jonothan Earnshaw has just been completed which examined differences of opinion from referees chosen by editors and those chosen by the authors themselves. In a nutshell – not a difference to matter. Eighty per cent of author-choice referees were already on the Journal panel of specialist referees and 7 per cent of referee choice was identical. We hope this study will be published in another journal after peer review.

The Editors

Colin Johnson will demit office in 1999 and Ronan O'Connell will join the team. We are grateful to Colin for his indefatigable work and enthusiasm and are pleased that he will continue to work with the Journal maintaining and strengthening European links and helping with further innovations and developments. We welcome Ronan to the editors' team and hope that he has signed a consent form and that his family has seen the patient information sheet!

The Electronic Era

The British Journal of Surgery website (www.bjs.co.uk) currently includes information about the Journal with details of BJS officers and Editorial Committee, instructions for authors, a list of forthcoming papers, free articles for downloading and information about research bursaries. It is expected that the website will also contain the 'BJS Scientific Surgery Archive', a collection of randomized trials published in the English language literature. A current selection from the archive is regularly published in the Scientific Surgery page of the Journal. This part of the website will eventually become more interactive and possible developments in the future include the maintenance of an active correspondence column, manuscript submission and refereeing, a full-text Journal available on the web, archiving of previous BJS volumes (currently presented on CD-ROM) and the development of sites for teaching and information.

The British Journal of Surgery does not wait for the new millennium to make significant change. The editors trust that these changes make the publication more attractive, reader-friendly and useful. The Journal is committed to growth and development and wishes to continue to serve the scientific surgical community. Your continued support is gratefully acknowledged and comments and criticisms are always welcome.

J. R. Farndon
J. A. Murie
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British Journal of Surgery 1998, 85, 1603–1604

Vascular gene therapy

The use of gene transfer as a therapeutic strategy is a rapidly emerging area of fundamental and applied medical research which has recently entered the phase of clinical trials. Gene therapy is the transfer of genetic material into somatic cells to effect changes in the pathogenetic processes which contribute to a disease[1]. Vascular gene therapy is at the forefront of this area as the first human trial of gene transfer has focused on patients with severe peripheral vascular disease.

The technology of gene transfer has advanced rapidly over the past few years. Currently there are two systems of transfer, *ex vivo* (indirect) and *in vivo* (direct). The former involves the removal and culture of host cells *in vitro* followed by insertion of the therapeutic gene into the cultured cells and, finally, the return of these genetically modified cells to the host. *In vivo* transfer involves direct site-specific introduction of the therapeutic gene into the host tissue. There are now a number of strategies for the transfer of DNA into mammalian cells. Exogenous genes may be inserted using viral and non-viral vectors by means of transfection or transduction. During transfection DNA is delivered to the cell by physical (microinjection, electroporation), chemical (liposomes) or virus-dependent mechanisms; transduction, on the other hand, uses retroviral vectors to effect this process.

Over the past few years gene transfer has been used to elucidate the pathophysiology of a number of diseases. These studies have led to the development of gene transfer as a therapeutic possibility for vascular disorders such as non-reconstructible critical limb ischaemia, graft failure, vessel restenosis and arterial thrombosis[2].

The first human trial of therapeutic angiogenesis is being conducted by Isner *et al.* and their first case was reported in the *Lancet* in 1996[3]. This report demonstrated the feasibility of using vascular endothelial growth factor (VEGF; a secreted endothelial cell mitogen that promotes angiogenesis) plasmid DNA transfer to augment collateral artery development in lower limb ischaemia. The method employed intra-arterial site-specific transfer of the DNA plasmid by incorporating it on to a hydrogel-coated angioplasty catheter. Angiogenesis was documented by both angiography and histology, and resulted in improvement of critical limb ischaemia.

The encouraging results noted with intra-arterial VEGF gene therapy have led to the first human phase I clinical trial of intramuscular phVEGF_{165} gene transfer in critical limb ischaemia[4]. All patients received a eukaryotic expression vector encoding the VEGF_{165} gene, transcriptionally regulated by the cytomegalovirus promoter/enhancer. As in the intra-arterial study, patients qualified for intramuscular gene therapy if two conditions were met. First, they had chronic critical limb ischaemia, including rest pain and/or non-healing ischaemic ulcers present for a minimum of 4 weeks without evidence of improvement in response to conventional therapies. Second, they were not optimal candidates for surgical or percutaneous revascularization. In Baumgartner and colleagues' recent report[4] on nine patients with ten critically ischaemic limbs treated by intramuscular gene therapy, evidence of new collateral vessels was associated with significant improvement in the ankle : brachial pressure index; ischaemic ulcer healing and successful limb salvage were also evident.

Failure of arterial bypass grafts remains a vexing problem for vascular surgeons. The cellular mechanisms leading to graft occlusion are fairly well established. Following graft placement, smooth muscle cell proliferation occurs, with subsequent migration of these cells into the intima where further proliferation and extracellular matrix deposition takes place. The clinical setting of saphenous vein bypass grafting lends itself admirably to *ex vivo* gene transfer techniques. The potential targets for this method of treatment include mediators of early graft failure, for instance expression of factors inhibiting platelet activation. Strategies may also be developed to modify smooth muscle cell or monocytic activity which modulate intimal hyperplasia and atherosclerosis, the causes of late graft failure.

Antiproliferative gene transfer techniques evaluated to date include the cytotoxic effect of transferring the viral thymidine kinase gene and the systemic administration of the prodrug ganciclovir. An evaluation has also been made of transfer of endothelial and inducible nitric oxide synthase and the inhibition of extracellular matrix degradation (which prevents the migration and proliferation of smooth muscle cells) by increasing the expression of tissue inhibitor of metalloproteinase[5]. Another promising technique involves the introduction of antisense oligonucleotides into a cell in order to inactivate the messenger RNA encoding proteins governing cellular hyperplasia. Mann *et al.*[6] have demonstrated that intraoperative gene therapy, using antisense oligonucleotide blockade of the expression of genes for two cell cycle regulatory proteins, prevents medial smooth muscle cell proliferation and the resultant autologous vein graft failure in an *in vivo* model. This technology is currently being evaluated in a clinical trial of infrainguinal vein bypass surgery[7]. The targets for gene transfer in postangioplasty restenosis are very similar, since cell activation and proliferation are key events in luminal narrowing following balloon dilatation of an artery.

Gene therapy for arterial thrombosis is another area of ongoing research, with encouraging results from preliminary studies. Several candidate genes for antithrombotic therapy have been identified, including those with antiplatelet activity (prostacyclin synthase, endothelial and inducible nitric oxide synthase), anticoagulant activity (hirudin, thrombomodulin) and fibrinolytic activity (tissue-type and urokinase-type plasminogen activators)[8]. In a primate model of graft thrombosis, Dichek *et al.*[9] have demonstrated a reduction of thrombus formation using grafts seeded with endothelial cells transduced with retroviral vectors encoding either of the above plasminogen activators.

Vascular gene therapy has moved rapidly from preclinical to human trials in the past few years. There remain, however, several questions regarding the safety and efficacy of this therapeutic strategy which involves the transfer of genetic material into host tissue. These issues are addressed in the stringent guidelines to which the human gene therapy protocols must adhere. Improvement in vector technology, coupled with a clearer understanding of the aetiology of vascular disease, will place gene therapy at the forefront of therapeutic intervention in the next century.

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Review

Radionuclide scanning in parathyroid diseases

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Background New radionuclide agents and scanning procedures have markedly improved preoperative parathyroid gland localization. The aim of this review was to evaluate the results of parathyroid scanning and to clarify its current place in the clinical management of parathyroid diseases.

Methods The literature describing the different radioisotopes and available scanning techniques was analysed and their clinical outcome in various parathyroid diseases was evaluated.

Results Using ^{99m}Tc-radiolabelled sestamibi or other ^{99m}Tc-labelled cationic complexes, parathyroid scintigraphy detects 87 per cent of solitary adenomas ($n = 894$), 55 per cent of abnormal glands in patients with multiglandular disease ($n = 303$) and 75 per cent of persistent or recurrent lesions in patients with previous neck surgery ($n = 240$). If necessary, three-dimensional imaging techniques can clarify the spatial localization of an ectopic uptake focus. The positive predictive value of the available scanning procedures is over 95 per cent, but false-positive uptake may be encountered.

Conclusion Radionuclide parathyroid gland scanning with ^{99m}Tc-labelled cationic complexes is the initial non-invasive method of choice for preoperative parathyroid gland localization in patients at special risk and/or with previous neck exploration. While scanning has also been proposed to facilitate parathyroidectomy, there is no objective evidence to support its routine use before a first-time surgical procedure.

In patients with primary hyperparathyroidism, bilateral neck exploration by an experienced parathyroid surgeon is curative in more than 95 per cent of cases[1] (98 per cent at the authors' institution[2]). Routine preoperative parathyroid imaging therefore is considered neither generally necessary nor cost-effective before a first parathyroidectomy[3]. Conversely, most experienced surgeons would consider preoperative parathyroid localization favourably in patients with previous neck surgery, even if multiple and sometimes invasive procedures were necessary[4]. Considerable efforts have been devoted to developing and improving imaging of abnormal parathyroid glands[5]. Within the past decade, new ^{99m}Tc-labelled radiopharmaceuticals as well as advanced technical scanning procedures have markedly enhanced parathyroid scanning[6–8]. Not surprisingly, these improvements reinitiated the classical controversy about the routine use of parathyroid gland imaging before a first parathyroidectomy.

In this article the literature describing the different scanning modalities available and their clinical usefulness is reviewed. An attempt is made to clarify the current place of radionuclide scanning in the clinical management of parathyroid diseases.

Radioisotopes

[^{201}Tl]thallium chloride

After early and deceptive attempts with agents such as ^{57}Co or ^{75}Se, clinically useful radionuclide scanning for parathyroid glands was first demonstrated in 1983 by Ferlin *et al.*[9] using a combined [^{201}Tl]thallium chloride and [^{99m}Tc]pertechnetate subtraction technique. Initially developed to study myocardial perfusion, thallium is an inorganic cation and a potassium analogue which enters cells through the transmembrane sodium–potassium adenosine 5′-triphosphatase pump[10]. Radionuclide scanning with [^{201}Tl]thallium chloride has been used widely to localize abnormal parathyroid tissue. Nevertheless, with a sensitivity in various series ranging from 26 to 68 per cent[5], this technique is not significantly superior to other currently used non-invasive imaging methods.

^{99m}Tc-radiolabelled sestamibi

^{99m}Tc-radiolabelled methoxyisobutylisonitrile (Cardiolite; Du Pont Pharma, Leo Ulis, France) or ^{99m}Tc-labelled sestamibi rapidly appeared to be a valuable tool for parathyroid gland localization[11] after Coackley *et al.*[12] incidentally reported the uptake and retention of this isonitrile derivative of pertechnetate in abnormal parathyroid tissue. Sestamibi is a monovalent lipophilic cation which diffuses passively through cell membranes and accumulates almost exclusively in mitochondria, following negative membrane potentials[10,13]. The exact mechanism of its elective uptake in abnormal parathyroid glands remains debatable. The higher blood perfusion and mitochondria content typically displayed by various tumour tissues with hypercellularity and increased cell metabolism are generally considered responsible for the uptake of sestamibi[14–16]. More recently, the role of *p*-glycoprotein, a membrane transport protein encoded by the multidrug resistance gene and responsible for cell exocytosis of various chemotherapeutic agents with structural homology to sestamibi, has also been observed in tumour cell lines[17] and confirmed in patients with various tumours[18]. The absence of *p*-glycoprotein in

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parathyroid adenomas, a unique feature among benign tumours, may account for ^{99m}Tc-labelled sestamibi uptake and positive scan results[19]. The favourable physical characteristics of ^{99m}Tc, including high-energy photons and short half-life, increase the definition of ^{99m}Tc-labelled sestamibi scanning and permit three-dimensional image acquisition. The use of ^{99m}Tc-labelled sestamibi also limits the radiation dosage delivered to the patient[20]. The clinical relevance of this new agent for parathyroid scanning has now been confirmed by numerous teams[4,15,21–54]. Several prospective comparative studies[11,37,41,45] have demonstrated its superiority over ^{201}Tl in the detection of abnormal parathyroid glands, including hyperplastic[11,55] and ectopic[56] glands. Ten years after its initial anecdotal description for parathyroid disease[57], ^{99m}Tc-labelled sestamibi is now considered to be the radionuclide of reference for parathyroid gland scanning.

Other ^{99m}Tc-labelled cationic complexes

Recently, the present authors[53], like others[58–62], have successfully tested another isonitrile derivative of pertechnetate: ^{99m}Tc-labelled 1,2-bis[bis(2-ethoxyethyl) phosphino]-ethane (Myoview, Amersham Laboratories, Courtaboeuf, France) or ^{99m}Tc-labelled tetrofosmin. This lipophilic cation, which is also a substrate of *p*-glycoprotein[63], accumulates in both the mitochondria and the cytoplasm of cells[10,13]. The uptake of ^{99m}Tc-labelled tetrofosmin in parathyroid tissue is similar to that of ^{99m}Tc-labelled sestamibi but the thyroid washout rate is slower[62]. The effective dose of absorbed radiation with ^{99m}Tc-labelled tetrofosmin is less than that of ^{99m}Tc-labelled sestamibi, and its preparation does not require heating. Preliminary clinical evaluation of this new tracer in patients with primary hyperparathyroidism has yielded results similar to those obtained with ^{99m}Tc-labelled sestamibi for parathyroid gland scanning with thyroid uptake subtraction[43,53,58,61]. A further recently described ^{99m}Tc-labelled cationic complex, ^{99m}Tc-labelled furifosmin, displays short retention in thyroid tissue and a shorter washout time from the thyroid gland. It may prove of particular value for parathyroid gland identification[64]. Although they still await further comparative evaluation, these new radionuclides may prove to be better alternatives to ^{99m}Tc-labelled sestamibi for parathyroid gland scanning[65].

Scanning methods

Single-isotope dual-phase scan

The simplest procedure was described in 1992 by Taillefer *et al.*[22] as the 'double phase study'. A single radioisotope scan is performed with cervicothoracic planar imaging, first at 15 min and also 1·5–3 h after injection of 15–25 mCi ^{99m}Tc-labelled sestamibi. Sestamibi accumulates in various tissues, including the parathyroid and thyroid, as early as a few minutes after intravenous administration[11]. After its administration, the ratio[11] of ^{99m}Tc-labelled sestamibi uptake in abnormal parathyroid glands to that in normal parathyroid glands is 10. This ratio increases to up to 35 for normal thyroid tissue, 40 for muscles, 80 for fat and 160 for blood[66]. Many parathyroid adenomas are clearly visible in the initial images, as early as 10–30 min after injection. ^{99m}Tc-labelled sestamibi uptake decreases rapidly in thyroid tissue but is retained within abnormal parathyroid tissue. Persistence of focal uptake on late imaging, 1·5–3 h after injection of the tracer, is highly indicative of the presence of an abnormal parathyroid gland. Interestingly, ^{99m}Tc-labelled tetrofosmin, which displays a slower washout from the thyroid (*Fig. 1*), yields inferior results to ^{99m}Tc-labelled sestamibi with the dual-phase technique[43,59]. Considering the kinetic properties of ^{99m}Tc-labelled sestamibi, some authors have successfully used a semiquantitative procedure during early dynamic series (factor analysis of dynamic structures) to differentiate thyroid and parathyroid structures[39,67,68]. The clinical relevance of this procedure awaits further evaluation[40].

Dual-isotope subtraction scan

The other method of overriding the background thyroid image when searching for abnormal parathyroid glands is to combine a ^{99m}Tc-labelled sestamibi scan with another scan, the latter acquired after administration of a second radionuclide specific to the thyroid. Subtraction of the two images as initially described with [^{201}Tl]thallium chloride[9] allows detection of focal uptake within the parathyroid glands. Numerous technical variants have been proposed. The most commonly used radionuclide for thyroid subtraction is ^{123}I. The thyroid scan is performed 2–24 h after intravenous or oral administration of the agent, although the timing and the order of the two scans varies between centres. Double-isotope acquisition with non-overlapping windows may also be used for simultaneous acquisition of both images[46]. To reduce the length of the dual-isotope technique, [^{99m}Tc]pertechnetate can be used to provide a thyroid image within 15 min; the results are comparable to those obtained with ^{123}I, but at a lower cost[25]. A computed subtraction procedure is used by many authors but requires the patient to remain immobile between the two scans and careful computed alignment of the images. In most cases, visual comparison of both thyroid and ^{99m}Tc-labelled sestamibi images is sufficient to distinguish abnormal parathyroid uptake from the thyroid background[14,43,69] (*Fig. 1*).

Three-dimensional studies

Until recently, most studies used only anterior planar acquisition for ^{99m}Tc-labelled sestamibi scanning of the parathyroid glands. The standard collimators with parallel holes allow the wide acquisition and exploration of all potential sites of ectopic parathyroid tissue, from salivary glands to myocardium. For the cervical area, a pin-hole collimator can be used selectively to improve the resolution[70]. The major drawback of anterior planar views is the lack of three-dimensional information which precludes spatial localization of the uptake. Combination of lateral or oblique planar views may help to unmask abnormal parathyroid glands from adjacent and/or superimposed structures[30,71]. ^{99m}Tc-labelled cationic complex scanning allows single photon emission computed tomography (SPECT) to be performed. With the help of the computed reconstruction of sagittal or transverse scans or even three-dimensionnal images, SPECT allows better localization of the uptake. It may therefore give valuable information to guide surgical exploration[32,34,41,44,69,72–74], especially when a focus of mediastinal uptake is observed on the planar anterior images. In this setting, SPECT allows easy differentiation of a middle mediastinal gland from a gland in the

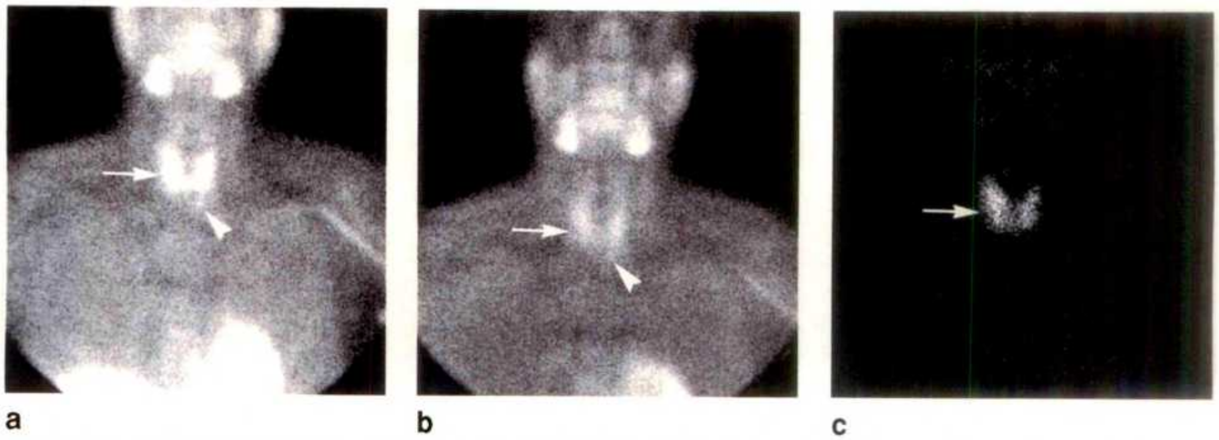

Fig. 1 Dual-phase and dual-isotope radionuclide scanning with ^{99m}Tc-labelled tetrofosmin and ^{123}I in a patient with primary hyperparathyroidism. A single focal uptake was visible (arrowhead) at the lower left pole of the thyroid (arrow) at **a** 20 min and **b** 2 h after administration of ^{99m}Tc-labelled tetrofosmin, but not on the thyroid scan 2 h after ^{123}I injection (**c**). Note the poor thyroid washout of ^{99m}Tc-labelled tetrofosmin on the delayed image (**b**). A single hyperplastic left inferior parathyroid gland weighing 60 mg was found during surgery and the patient remains normocalcaemic 1 year later

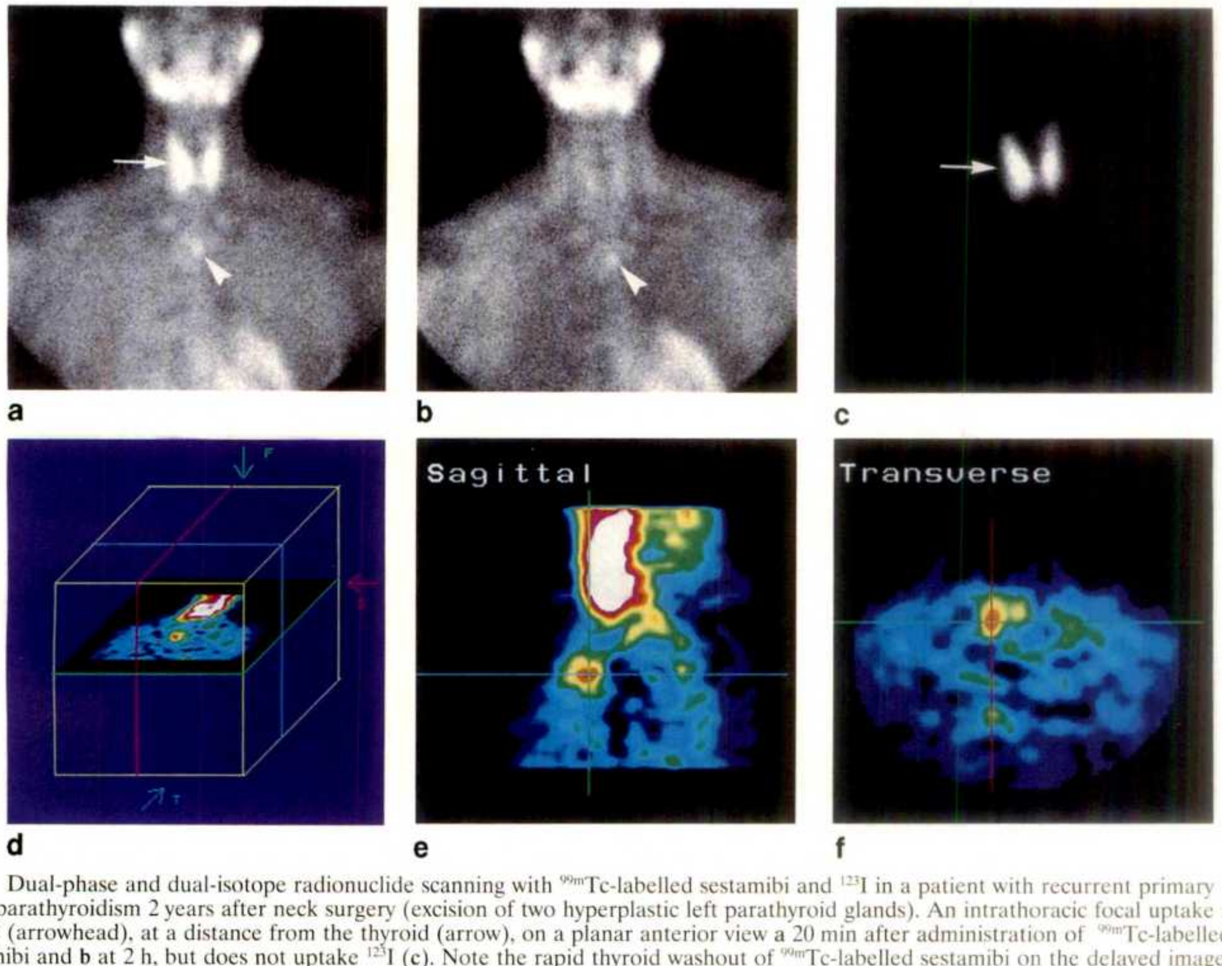

Fig. 2 Dual-phase and dual-isotope radionuclide scanning with ^{99m}Tc-labelled sestamibi and ^{123}I in a patient with recurrent primary hyperparathyroidism 2 years after neck surgery (excision of two hyperplastic left parathyroid glands). An intrathoracic focal uptake is visible (arrowhead), at a distance from the thyroid (arrow), on a planar anterior view **a** 20 min after administration of ^{99m}Tc-labelled sestamibi and **b** at 2 h, but does not uptake ^{123}I (**c**). Note the rapid thyroid washout of ^{99m}Tc-labelled sestamibi on the delayed image (**b**). **d–f** Single photon emission computed tomography with **e** sagittal and **f** transverse scans located this uptake behind the sternum within the anterior mediastinum (intersecting lines). At surgery, a fifth hyperplastic parathyroid gland weighing 240 mg was found within the left thoracic thymus and removed through a cervicotomy. This patient is normocalcaemic 2 years after surgery

thyrothymic fat (*Fig. 2*) or from a non-specific uptake such as an inflammatory lesion within the sternal manubrium (*Fig. 3*). On the other hand, the routine use of SPECT in patients with primary hyperparathyroidism, as advocated by Billotey *et al.*[39] and Sfakianakis and colleagues[32], provided only marginal improvement in the overall detection rate of abnormal parathyroid glands when compared prospectively with standard planar imaging techniques[34,41,69].

Intraoperative detection

When a ^{99m}Tc-labelled cationic complex is injected immediately before surgery, intraoperative scintimetry with a hand-held γ probe may also provide intraoperative guidance for neck exploration and detection of abnormal parathyroid tissue[5,75,76]. Despite potential uptake in thyroid nodules[75], a high sensitivity of this promising method has already been described in preliminary studies on parathyroid adenomas[75], and on carcinomas and their metastatic spread to lymph nodes[75] and subcutaneous tissue[5]. Immediate preoperative 'nuclear mapping' by percutaneous scintimetry has recently been proposed to delineate the abnormal gland(s) and limit the extent of surgery in patients with hyperparathyroidism[77]. Further clinical experience with these techniques is necessary to confirm their clinical relevance.

Localization of abnormal parathyroid glands

Since its initial description, numerous series have confirmed the value of parathyroid gland radionuclide scans with ^{99m}Tc-labelled sestamibi. Nevertheless, in line with the prediction of Doppman, the initial enthusiastic reports of ^{99m}Tc-labelled sestamibi scintigraphy in limited series have been progressively tempered by accumulating experience[21]. Indeed, the reported sensitivity of ^{99m}Tc-labelled sestamibi scanning varies considerably within the series as well as with the type of parathyroid disease examined. To estimate the overall sensitivity of parathyroid scanning with ^{99m}Tc-labelled complexes for solitary adenomas, multiglandular disease, persistent or recurrent hyperparathyroidism, and parathyroid carcinoma, the literature indexed in the Medline database from 1989 has been reviewed and the results of those studies reported in sufficient detail have been combined.

Parathyroid adenomas

Like other parathyroid localization techniques[5], the best results of ^{99m}Tc-labelled sestamibi scanning are observed with solitary adenomas which account for more than 80 per cent of cases of primary hyperparathyroidism. In this setting, prospective studies comparing the sensitivity of ^{99m}Tc-labelled sestamibi scanning with other non-invasive parathyroid imaging studies confirm its superiority over computed tomography[78], high-resolution ultrasonography[29,41,42,60,79] and magnetic resonance imaging[16,60,78].

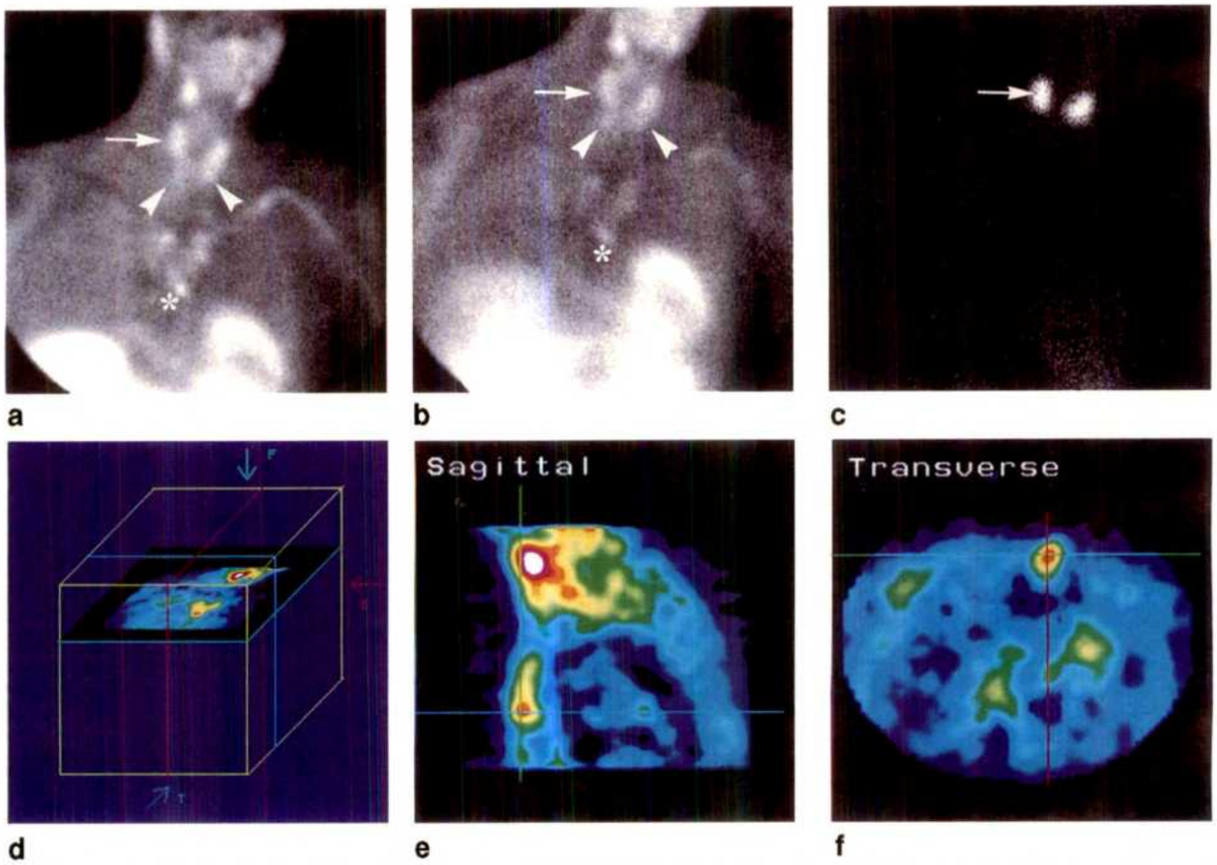

Fig. 3 Dual-phase and dual-isotope radionuclide scanning with ^{99m}Tc-labelled tetrofosmin and ^{123}I in a patient with a past history of ankylosing spondylitis and primary hyperparathyroidism occurring 2 years after previous partial thyroidectomy. On planar anterior views two cervical focal uptakes are visible at both inferior poles of the thyroid (arrowheads) at **a** 20 min and **b** 2 h after administration of ^{99m}Tc-labelled tetrofosmin and not on the thyroid scan 2 h after ^{123}I injection (**c**). A third median thoracic focus is also visible on planar views (*). **d–f** Single photon emission computed tomography with **e** sagittal and **f** transverse scans located this uptake (intersecting lines) within the sternal manubrium. Only one right inferior hyperplastic parathyroid gland weighing 132 mg was found at surgery and removed. This patient remains normocalcaemic 18 months after surgery

Table 1 Sensitivity of ^{99m}Tc-radiolabelled sestamibi scanning for solitary adenoma

Reference	Year	Scanning technique	No. of patients	Sensitivity (%)
O'Doherty *et al.*[11]	1992	DI (^{123}I)	40	98
Wei *et al.*[21]	1992	DI (^{123}I)	11	100
Taillefer *et al.*[22]	1992	DP	21	90
Thulé *et al.*[24]	1994	DI (^{123}I)	14	93
Wei *et al.*[25]	1994	DI (^{99m}Tc)	13	92
Irvin *et al.*[26]	1994	DP	17	94
Billy *et al.*[29]	1995	DP	12	83
Lee *et al.*[15]	1995	DP	30	93
Sfakianakis *et al.*[32]	1996	DP, SPECT	52	96
McHenry *et al.*[34]	1996	DP, DI (^{123}I), SPECT	95	81
Johnston *et al.*[35]	1996	DI (^{99m}Tc)	36	89
Malhotra *et al.*[36]	1996	DP, DI (^{99m}Tc)	26	100
Rauth *et al.*[37]	1996	DP	14	93
Martin *et al.*[38]	1996	DP	50	82
Blocklet *et al.*[40]	1997	DP	32	84
Staudenherz *et al.*[41]	1997	DP, SPECT	52	78
Bonjer *et al.*[42]	1997	DP, SPECT	21	81
Fjeld *et al.*[43]	1997	DI (^{99m}Tc)*	16	80
Neumann *et al.*[44]	1997	DP, SPECT	47	55
Bergenfelz *et al.*[45]	1997	DI (^{99m}Tc)	36	86
Hindié *et al.*[46]	1997	DI (^{123}I)	59	95
Sinha *et al.*[47]	1997	DP	19	89
Caixas *et al.*[49]	1997	DP	64	100
Carter *et al.*[50]	1997	DP	14	86
Shen *et al.*[51]	1997	n.a.	28	71
Pattou *et al.*[53]	1998	DP*, DI (^{123}I)	75	87
Overall			894	87

* ^{99m}Tc-labelled sestamibi and/or ^{99m}Tc-labelled tetrofosmin. DI (^{123}I), dual-isotope subtraction scan with ^{99m}Tc-labelled sestamibi and ^{123}I; DI (^{99m}Tc), dual-isotope subtraction scan with ^{99m}Tc-labelled sestamibi and ^{99m}Tc; DP, single-isotope dual-phase scan with ^{99m}Tc-labelled sestamibi; SPECT, routine use of single photon emission computed tomography; n.a., not available

The only non-invasive technique which appears superior to ^{99m}Tc-labelled sestamibi scanning for adenoma detection is positron emission tomography (PET)[80]. Although PET with 2-[f-18]-fluoro-2-deoxy-D-glucose[81,82] or L-[^{11}C]methionine[83,84] appears promising for parathyroid gland localization, it is expensive and still not widely available; it can also give false-negative and false-positive findings[85,86]. The clinical relevance of PET requires further evaluation.

Despite reports of ^{99m}Tc-labelled sestamibi scanning providing a near 100 per cent sensitivity[11,21,36,49], false-negative scans can occur with cervical adenomas and ectopic lesions[34,53]. Assessing the overall clinical experience from the literature (*Table 1*), it is estimated that at least one in eight solitary parathyroid adenomas (13 per cent) is not detected with ^{99m}Tc-labelled sestamibi scanning. The exact cause for these rare but frustrating negative scans is not clearly understood.

In most series, the sensitivity of parathyroid scanning grossly correlates with the weight of the glands. Nevertheless, positive scans are frequently observed for lesions weighing less than 200 mg[46]. In the authors' experience, the smallest glands detected weighed 118 mg with ^{99m}Tc-labelled sestamibi and 60 mg with ^{99m}Tc-labelled tetrofosmin (*Fig. 1*). On the other hand, like others[11,14], the authors have already found parathyroid adenomas weighing several grams in patients with negative preoperative ^{99m}Tc-labelled sestamibi scans. Similarly, cystic adenomas are unlikely to be detected by scintigraphy[16]. The size of abnormal parathyroid glands does not represent the only determinant for ^{99m}Tc-labelled sestamibi uptake.

The anatomical location of parathyroid adenomas, especially within the thyroid uptake area, clearly hinders their detection and may increase the occurrence of false-negative scans[41]. Planar anterior views may also yield false negatives when the adenoma is located ectopically, within the oesophagotracheal groove[30], or behind a vascular[61] or osseous[16] structure. Similarly, undescended inferior parathyroid glands cannot easily be differentiated from an adjacent salivary gland without lateral or oblique views (authors' unpublished observations). For these equivoqual cases, three-dimensional imaging procedures improve the sensitivity of ^{99m}Tc-labelled sestamibi scanning[34,39] and appear of particular value[71]. Among the various pathological criteria, hypervascularity[15,16] and mitochondrial richness[14] of the parathyroid specimen are significantly related to the positive uptake of ^{99m}Tc-labelled sestamibi. However, the oxyphilic nature of the lesion does not seem critical[14,41,60]. As already mentioned, the role of *p*-glycoprotein expression in patients with false-negative scans is under investigation[19,87].

Technical shortcomings may further explain false-negative results. Few prospective studies have compared single-isotope (dual phase) and dual-isotope subtraction scanning procedures, but the latter have been shown slightly to improve the sensitivity of sestamibi scanning for adenomas[29,30,69]. The rapid washout of ^{99m}Tc-labelled sestamibi from some abnormal parathyroid glands may impair their detection on the delayed image of a dual-phase scan[30,88,89]. Conversely, the unusual uptake of [^{99m}Tc]pertechnetate by hypervascular parathyroid adenomas may hinder the interpretation of dual-isotope scans in cases of intrathyroidal ectopic parathyroid glands[90,91]. Although the dose of ^{99m}Tc-labelled sestamibi varies from 5 to 25 mCi in reported series, sensitivity appears enhanced when more than 15 mCi is administered[27].

Ultimately, the experience of the nuclear medicine team in parathyroid gland scanning remains a major determinant for the successful detection of abnormal glands.

Multiglandular disease

Parathyroid disease is multiglandular in 10–20 per cent of patients with sporadic primary hyperparathyroidism[92]. Hyperplasia of all parathyroid glands is frequent in familial hyperparathyroidism and virtually constant in secondary or tertiary disease. Localization of these hyperplastic glands is notoriously difficult with any parathyroid imaging technique[5], including scanning with ^{99m}Tc-labelled cationic complexes. In patients with multiglandular disease, hardly more than half of abnormal parathyroid glands (55 per cent) are detected with available scanning procedures (*Table 2*). Preoperative detection of all pathological glands occurs in only 29 per cent of patients. As for adenomas, the size of hyperplastic glands generally correlates with the positivity of sestamibi scanning although discrepancies may be observed[33,93]. The risk of rapid washout of ^{99m}Tc-labelled sestamibi from hyperplastic glands may also limit their detection with a single-isotope double-phase study[89]. Uptake of ^{99m}Tc-labelled sestamibi by bilateral giant hyperplastic glands may also mimic thyroid uptake[68] and so routine thyroid

Table 2 Sensitivity of ^{99m}Tc-radiolabelled sestamibi scanning for multiglandular hyperparathyroidism

Reference	Year	Aetiology	Scanning technique	No. of patients	No. of glands	Sensitivity (%)	
						Patients*	Glands
O'Doherty *et al.*[11]	1992	I, II	DI (^{123}I)	15	60	n.a.	53
Wei *et al.*[21]	1992	I, II	DI (^{123}I)	9	30	n.a.	67
Wei *et al.*[25]	1994	I, II	DI (^{99m}Tc)	17	46	n.a.	76
Thompson *et al.*[27]	1994	I	DI (^{99m}Tc)	18	n.a.	55	n.a.
Lee *et al.*[15]	1995	I, II	DP	9	30	11	60
Sfakianakis *et al.*[32]	1996	I, II	DP, SPECT	5	17	60	88
Piga *et al.*[33]	1996	I	DP	9	27	n.a.	44
Johnston *et al.*[35]	1996	I	DI (^{99m}Tc)	6	14	50	71
Malhotra *et al.*[36]	1996	I, II	DP, DI (^{99m}Tc)	18	69	28	52
Martin *et al.*[38]	1996	I	DP	11	29	n.a.	31
Blocklet *et al.*[40]	1997	II	DP	21	62	57	76
Hindié *et al.*[46]	1997	I	DI (^{123}I)	6	15	67	80
Caixas *et al.*[49]	1997	I, II	DP	23	n.a.	17	n.a.
Shen *et al.*[51]	1997	I	n.a.	12	40	8	28
Chesser *et al.*[52]	1997	II	n.a.	12	46	n.a.	83
Pons *et al.*[93]	1997	II	DP	20	64	n.a.	54
Pattou *et al.*[53]	1998	I	DP†, DI (^{123}I)	25	56	16	41
Ishibashi *et al.*[54]	1998	II	DP	17	61	n.a.	70
Proye *et al.*‡	1998	II	DP†, DI (^{123}I)	50	192	18	41
Overall				303	858	29	55

*Proportion of patients in whom all abnormal glands were detected; †^{99m}Tc-labelled sestamibi and/or ^{99m}Tc-labelled tetrofosmin; ‡unpublished data; §overall sensitivity was calculated for patients for whom the information was available ($n = 193$). I, Primary hyperparathyroidism; II, secondary or tertiary hyperparathyroidism; DI (^{123}I), dual-isotope subtraction scan with ^{99m}Tc-labelled sestamibi and ^{123}I; DI (^{99m}Tc), dual-isotope subtraction scan with ^{99m}Tc-labelled sestamibi and ^{99m}Tc; DP, single-isotope dual-phase scan with ^{99m}Tc-labelled sestamibi; SPECT, routine use of single photon emission computed tomography; n.a., not available

subtraction with a dual-isotope procedure is preferred. In patients with renal failure and secondary hyperparathyroidism, the comparison of morphological and functional data suggests a correlation of sestamibi uptake in parathyroid tissue with its autonomous hyperfunction[33]. Occasionally, when total parathyroidectomy and autotransplantation in the forearm have been performed, radionuclide scanning can successfully detect the ectopic graft and confirm its function[15,16,27,94].

Persistent or recurrent hyperparathyroidism

When hyperparathyroidism persists or recurs after previous neck surgery, scarring and distortion of normal tissues, as well as a high frequency of ectopic lesions, render surgical neck exploration difficult. With a sensitivity varying between 59 and 100 per cent (*Table 3*), ^{99m}Tc-labelled cationic complexes have also significantly improved the results of parathyroid gland scanning in these patients. The overall sensitivity of this technique (75 per cent) compares favourably with that of all other non-invasive tools available for parathyroid gland localization in reoperative cases[5]. As ectopic lesions are frequent in such a setting, SPECT and the generation of three-dimensional images are highly desirable[30,39,69,74]. After a failed neck exploration, postoperative inflammation can delay the thyroid washout of the radionuclide for a few weeks. Scanning should therefore be appropriately scheduled to avoid the early postoperative period; if it is not carried out within 48 h of surgery[95], it should be delayed for a few months[96].

Parathyroid carcinomas

Malignant transformation is found in less than 1 per cent of patients operated on for primary hyperparathyroidism; it may cause the metastatic spread of parathyroid cells. Few cases of parathyroid carcinoma scanning with ^{99m}Tc-labelled sestamibi have been reported[25,34,97,98]. All malignant glands were detected accurately, including their metastases[5,35]. However, the present authors have

Table 3 Sensitivity of ^{99m}Tc-radiolabelled sestamibi scanning for persistent or recurrent hyperparathyroidism

Reference	Year	Scanning technique	No. of patients	Sensitivity* (%)
Weber *et al.*[23]	1993	DI (^{123}I)	12	83
Thompson *et al.*[27]	1994	DI (^{99m}Tc)	37	62
Chen *et al.*[30]	1995	DP	35	59
Majors *et al.*[31]	1995	DI (^{99m}Tc), DI (^{123}I)	9	100
Jaskowiak *et al.*[4]	1996	DI (^{123}I)	39	67
Johnston *et al.*[35]	1996	DI (^{99m}Tc)	12	75
Malhotra *et al.*[36]	1996	DP, DI (^{99m}Tc)	7	71
Billotey *et al.*[39]	1996	DP, SPECT	33	87
Bonjer *et al.*[42]	1997	DP, SPECT	6	100
Neumann *et al.*[44]	1997	DP, SPECT	11	91
Fayet *et al.*[48]	1997	DP	18	78
Caixas *et al.*[49]	1997	DP	7	100
Proye *et al.*†	1998	DP‡, DI (^{123}I), SPECT	14	79
Overall			240	75

*Proportion of patients in whom all abnormal glands were detected; †updated from Reference 2; ‡^{99m}Tc-labelled sestamibi or ^{99m}Tc-labelled tetrofosmin. DI(^{123}I), dual-isotope subtraction scan with ^{99m}Tc-labelled sestamibi and ^{123}I; DI(^{99m}Tc), dual-isotope subtraction scan with ^{99m}Tc-labelled sestamibi and ^{99m}Tc; DP, single-isotope dual-phase scan with ^{99m}Tc-labelled sestamibi; SPECT, routine use of single photon emission computed tomography observed one malignant parathyroid lesion without any focal uptake on a ^{99m}Tc-labelled tetrofosmin scan (unpublished observation). Eventually, multiple areas of ^{99m}Tc-labelled sestamibi skeletal uptake may be noted in patients with parathyroid carcinoma. They are generally due to locally destructive and hypervascularized lesions of osteitis fibrosa cystica (brown tumours) rather than to an osseous metastasic spread.[98]

False-positive uptake

The goals of preoperative parathyroid gland localization are to guide neck exploration, particularly after previous neck surgery, and to shorten the operation, especially in fragile patients. False-positive results are a major drawback because they can mislead the inexperienced surgeon and result in surgical failure, even in patients with a cervical adenoma[35]. They may also lead to unnecessary invasive surgery when indicating an ectopic uptake focus[99].

In the absence of an adequately designed study, the rate of false-positive uptake of ^{99m}Tc-labelled sestamibi in normal parathyroid tissue and the specificity of parathyroid scanning can not be ascertained with accuracy. The specificity of ^{99m}Tc-labelled sestamibi scanning for the detection of abnormal parathyroid tissue is frequently assumed to exceed 95 per cent[25,100]. In patients with hyperparathyroidism, either primary or secondary, the positive predictive value of a focal uptake for the presence of an abnormal gland (clinical reflection of the specificity) is over 95 per cent in most series[24,25,100]. Nevertheless, one should be aware that ^{99m}Tc-labelled sestamibi also accumulates in numerous non-parathyroidal tissues. Because coexisting primary hyperparathyroidism and neoplasia are commonly encountered[101], it is noteworthy that various primary tumours including breast[102], lung[103], and head and neck carcinomas[104], as well as their lymph node or osseous metastases[104], can take up ^{99m}Tc-labelled sestamibi. Within the neck, uptake and prolonged retention of ^{99m}Tc-labelled cationic complexes have also been described in differentiated thyroid malignancies including follicular[105], papillary[106] and Hürthle cell[107] carcinomas, and primary thyroid lymphomas[108]. Focal uptake can also be observed in common inflammatory diseases such as arthritis (*Fig. 3*) and tuberculosis[109], as well as in other granulomatosis potentially associated with hypercalcaemia such as sarcoidosis[110].

In patients with primary hyperparathyroidism, the most commonly encountered source of a false-positive result is the coexistence of benign thyroid disease. With a double-phase study, solitary thyroid adenomas[105] and multinodular goitres may exhibit abnormal retention of ^{99m}Tc-labelled sestamibi and mimic the uptake of orthotopic parathyroid tissue. Such thyroid abnormalities may be present in more than one-third of patients with primary hyperparathyroidism[41]. Their detection through careful physical examination and/or ultrasonography is essential before interpreting a ^{99m}Tc-labelled sestamibi scan. In patients with partially inhibited thyroid function due to iodine contamination or thyroxine treatment, suppressed thyroid nodules often retain their ability to take up ^{99m}Tc-labelled sestamibi. They may be falsely identified as parathyroid tissue when a subtraction study is performed. Non-specific ^{99m}Tc-labelled sestamibi uptake in brown tumours has also been described in patients with osteitis fibrosa secondary to benign[89] or malignant[98] parathyroid disease. Non-parathyroid tumoral uptake of ^{99m}Tc-labelled sestamibi may be observed in thymic lesions such as thymoma (authors' unpublished observation) and carcinoid[111]. In the setting of multiple endocrine neoplasia, pituitary adenoma may be also depicted during ^{99m}Tc-labelled sestamibi scanning[111]. Other lesions shown to retain ^{99m}Tc-labelled sestamibi and to produce false-positive scan results include lymph nodes[32,34], sarcoid nodules[15,16] and non-Hodgkin lymphomas[32]. In such situations, concurrent scintigraphy performed after the injection of other tumour-imaging agents which do not accumulate in parathyroid adenomas, such as ^{67}Ga or ^{111}In-radiolabelled octreotide, may be helpful in identifying non-specific ^{99m}Tc-labelled sestamibi uptake[32,112].

Indications for parathyroid scanning

Like Mitchell *et al.*[7], as a technique to enable the preoperative localization of abnormal parathyroid glands, the authors strongly believe that parathyroid scanning with ^{99m}Tc-labelled cationic complexes should be considered only in patients with a proven clinical and biochemical diagnosis of hyperparathyroidism. Radionuclide scanning should not be used to confirm the diagnosis of hyperparathyroidism or to influence the choice of surgical treatment in equivocal cases.

Before a first neck exploration

Until recently, most authors agreed that preoperative localization of parathyroid glands was rarely indicated in patients without previous neck surgery[3]. However, as it has significantly improved the results of parathyroid gland imaging, an increasing number of authors now advocate the routine use of preoperative ^{99m}Tc-labelled sestamibi scanning in all patients with hyperparathyroidism[8,28,34–36,46,57,100,113,114]. The rationale of this strategy is to improve the results of surgical treatment of the disease, to decrease its associated morbidity and to reduce the overall cost of management.

In patients with sporadic primary hyperparathyroidism, routine bilateral neck exploration by an experienced surgeon is curative in over 95 per cent of cases with a morbidity rate of less than 2 per cent[1,115]. One can hardly expect to improve on this outstanding result using a preoperative parathyroid gland localization technique with a sensitivity of less than 90 per cent. There is also little doubt that widespread application of routine parathyroid scanning will encourage surgeons with less experience in parathyroidectomy to embark on this demanding operation[50]. Preoperative parathyroid scanning would indeed help these surgeons to find solitary parathyroid adenomas and successfully treat primary hyperparathyroidism in approximately 80 per cent of patients. Successful parathyroidectomy will, however, remain a difficult challenge in the 10–20 per cent of more demanding cases, especially those with multiglandular disease for which scanning is of little help. One might, therefore, speculate that routine scanning, by increasing the proportion of operations performed by inexperienced surgeons, might diminish rather than enhance the excellent overall results of parathyroid surgery.

One clear benefit of routine parathyroid radionuclide scanning might be the preoperative identification of rare ectopic adenomas lying within the anterior or mid mediastinum which are not accessible from the neck. In this case, some authors even propose exploration of the chest during the initial operation if cervical exploration is negative[56,116]. However, the cost effectiveness of routine detection of ectopic parathyroid glands with radionuclide scanning before every first parathyroidectomy remains questionable. One must consider the very low frequency of such lesions (1–2 per cent)[117] and the risk of not detecting them if present (13 per cent). Moreover, the risk of false-positive uptake should also be remembered before embarking on a major procedure during the first operation[99].

Because a solitary adenoma is found in over 80 per cent of patients with sporadic primary hyperparathyroidism, some authors now support alternative and potentially less invasive surgical approaches. In the unilateral approach, surgery is terminated when one abnormal and one normal ipsilateral gland have been identified on the first side explored[118,119]. Without any preoperative localization procedure, the proportion of patients who undergo a unilateral neck exploration with this approach is only 34–48 per cent[51,114,120]. Using [^{201}Tl]thallium chloride preoperative scanning, unilateral exploration may be performed in half the patients[121]. The routine use of preoperative parathyroid scanning with ^{99m}Tc-labelled cationic complexes enhances this proportion to 63–70 per cent[46,51,53,114]. Conversely, parathyroid scanning only slightly decreases the theoretical risk of missing a contralateral second abnormal gland, estimated at 10 per cent[51,53,120]. To avoid this potential pitfall, the combination of preoperative parathyroid scanning and intraoperative hormone measurement has been proposed[26,32,114,122]. Most authors who advocate these less invasive approaches now also advocate the routine use of parathyroid preoperative imaging. Comparative studies of such alternative approaches with the standard technique of bilateral exploration have shown a 30-min decrease in the mean operating time[26,32,46,50,113,123]. Consequently, the major claim of the proponents of this alternative strategy is to improve the cost-effectiveness of treatment. Unfortunately this claim relies on theoretical[124] or retrospective[26,113,123] studies with many potential biases. It has not been confirmed in a prospective study[114] and remains highly controversial[51,125]. In reality, the true savings in operative costs of a unilateral neck exploration are difficult to quantify and must be carefully balanced in controlled prospective studies with the cost and burden of routine radionuclide scanning[7,51].

It is the authors' opinion that objective evidence of the benefit of routine parathyroid scanning, in terms of efficiency, safety and/or cost effectiveness of surgical treatment of primary hyperparathyroidism, has not been clearly established. In some cases it may even be misleading and responsible for failure to cure patients with solitary cervical adenomas[126]. Like most others[7,34,47,51], the present authors continue to believe that preoperative parathyroid localization is not necessary before a first-time parathyroidectomy[127]. The only exception to this is the fragile patient[91] who would clearly benefit from a shortened, guided, minimal exploration, occasionally under local anaesthesia[128]. For these patients, radionuclide scanning with ^{99m}Tc-labelled cationic complexes such as ^{99m}Tc-labelled sestamibi or ^{99m}Tc-labelled tetrofosmin is the initial localization procedure of choice.

For patients with familial or secondary hyperparathyroidism, standard bilateral neck exploration and thymectomy are mandatory to recognize and cure multiglandular disease[129]. If one considers the poor results of all scanning techniques in the detection of hyperplastic parathyroid glands, as well as their frequent failure to recognize multiglandular disease, there seems to be little place for preoperative parathyroid scanning in this setting.

Patients with previous neck surgery

The morbidity of neck exploration greatly increases in the face of previous cervical surgery[2]. The frequency of ectopic and in some cases extracervical abnormal parathyroid gland(s) is also enhanced when hyperparathyroidism persists or recurs after an unsuccessful surgical attempt at cure. In this situation preoperative localization of the parathyroid glands with various imaging procedures, often combined with invasive tests, appears mandatory to increase the chances of successful reoperation[4]. Uptake of ^{99m}Tc-labelled sestamibi is observed in nearly 75 per cent of these elusive lesions. When ^{99m}Tc-labelled sestamibi scanning is coupled with other complementary morphological studies, such as high-resolution ultrasonography and/or magnetic resonance imaging, most abnomal parathyroid gland(s) can be detected before reoperation in patients with persistent or recurrent disease[4,16,48,130]. It is probable that within a few years this approach will significantly decrease the need for invasive localization procedures such as selective venous sampling for parathyroid hormone measurement[4]. In selected cases, when three-dimensional imaging precisely localizes a unique abnormal gland within the neck, ^{99m}Tc-labelled sestamibi scanning without any concurrent morphological localization studies may even be sufficient for preoperative localization in patients with previous neck surgery. In the difficult setting of recurrent or persistent disease after total parathyroidectomy and ectopic autotransplantation, parathyroid scanning may prove to be the ultimate tool allowing functional assessment to document the role of the grafted tissue[94]. Further experience may confirm that intraoperative scintigraphic detection can optimize the chances of surgical cure in the most difficult cases.

Conclusion

^{99m}Tc-labelled cationic complexes and improvement in technical imaging procedures have significantly enhanced the performance of radionuclide parathyroid scanning, especially for solitary adenomas. Radionuclide scanning has become the initial non-invasive study of choice when parathyroid gland localization is necessary before parathyroidectomy; this is generally for fragile patients and reoperative cases. In this setting, the authors recommend performing early and delayed double-phase imaging with ^{99m}Tc-labelled sestamibi plus a thyroid subtraction scan with ^{123}I or ^{99m}Tc, and anterior and oblique planar views in all cases. When needed, three-dimensional imaging by SPECT can clarify the spatial localization of an abnormal uptake focus. Parathyroid gland scanning has also been proposed to facilitate less invasive approaches for parathyroidectomy. However, favourable outcome and cost effectiveness of these alternative approaches have not been established; objective evidence is still lacking to support routine parathyroid gland scanning before a first-time parathyroidectomy.

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Review

Solitary rectal ulcer syndrome

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Background Solitary rectal ulcer syndrome is a rare disorder characterized by erythema or ulceration of the rectal wall, associated with typical histological features, and disturbed defaecatory behaviour with the passage of blood and mucus.

Methods This is a review based on a literature search using a computer database (Medline) and manual cross-referencing.

Results The pathogenesis is likely to vary in different patients; it includes trauma from straining, direct digital trauma and possibly primary neuromuscular pathology. The histological findings of extension of the muscularis mucosa between crypts and muscularis propria disorganization on full-thickness specimens are characteristic. Biofeedback defaecation retraining, including habit training, can lead to symptom improvement and return to work in a majority of patients. Abdominal rectopexy offers long-term symptom improvement in approximately 50 per cent of patients. Rectal ulceration may persist after any treatment, even if symptoms improve.

Conclusion Behavioural therapy and carefully considered operations offer the best treatment results. Further work on psychological factors and neuromuscular and vascular pathology is required.

The term 'solitary rectal ulcer syndrome' (SRUS) is used to describe a spectrum of clinicopathological abnormalities which can affect both adults and children. The aetiology remains obscure. Macroscopic ulceration is not invariably present. The cardinal feature is isolated erythema or ulceration of a part of the rectal wall, although the syndrome also incorporates abnormal defaecatory behaviour and the passage of blood and mucus. The condition is rare and so misdiagnosis of inflammatory bowel disease or cancer is common, although the histology is characteristic[1]. There is a variable response to therapy.

Although first described in 1829[2] the first significant publication occurred in 1969 when the clinicopathological features were defined for the first time[3]. This review of the literature was undertaken using Medline, for the period 1986 to 1998, using the keywords 'solitary rectal ulcer syndrome'. A manual cross-referencing was also done. Based on these methods, only those references considered of interest or thought to contain well validated new information were included; no attempt was made to include all identified references. In conjunction with the above, details of recent studies from the authors' own institution were also considered.

Clinical features

Delayed or incorrect diagnosis of SRUS has been the subject of many papers[4–8]. SRUS presents as a disorder of defaecation with the following typical features[9].

1 Passage of blood and mucus from the rectum associated with straining and a feeling of incomplete emptying.

2 Evidence of rectal prolapse, either internal or external, with or without abnormal perineal descent on evacuation proctography.

3 Sigmoidoscopic appearance varying from erythema to ulceration or polypoid lesions. These are commonly solitary but may be multiple. Although most commonly on the anterior rectal wall, they may be more extensive and even circumferential.

4 Histological evidence of fibrous obliteration of the lamina propria with disorientation of the muscularis mucosa and extension of smooth muscle fibres into the lamina propria.

There is a general lack of awareness of the syndrome as a direct result of its rarity; the incidence of SRUS was estimated at one in 100 000 per year in a 10-year study in Northern Ireland[9]. Retrospective analyses have demonstrated that up to 26 per cent of patients with SRUS are initially misdiagnosed[10]. Ulcerated SRUS may be mistaken for inflammatory bowel disease, and some patients have been treated with high-dose oral steroids[10]. Polypoid lesions may be confused with neoplasia. Histological examination, therefore, plays a key role in diagnosis, as the proctoscopic appearance can be misleading.

The syndrome affects men and women in approximately equal proportions; two retrospective series of 80[1] and 45[11] patients respectively reported a female predominance, while another two series[12,13] reported a slight male predominance. Although typically described as affecting young adults[2], the condition is also seen in children, adolescents and the elderly. The mean age of presentation was 49 years in one series with up to 25 per cent of patients presenting over the age of 60 years[1]. In that report, rectal bleeding was documented in 56 per cent, straining in 28 per cent, passage of mucus in 18 per cent, and constipation or diarrhoea in 55 per cent of patients. A surprising 26 per cent of patients were asymptomatic[1]. In

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another report rectal bleeding was almost universal (98 per cent), as was passage of mucus (96 per cent) and a feeling of unsatisfied defaecation (93 per cent); diarrhoea was reported in 20 per cent and constipation in 49 per cent[9]. A sense of incomplete defaecation is common, and patients may spend more than an hour at each visit to the toilet[14].

Patients often present long after the onset of symptoms. The mean reported duration of symptoms before diagnosis ranges from 3·5 to 5·3 years[1,9,15]. The variable clinical presentation in different series may reflect variations in referral to either surgical or medical specialist centres. Most of the reported series are retrospective, and some of these document asymptomatic patients in whom screening endoscopy has detected SRUS. Those in whom the syndrome is associated with external rectal prolapse are more often referred to surgeons than to physicians.

Diagnosis can usually be made on sigmoidoscopy. Ulceration is not universally present, with polypoid, non-ulcerated lesions and erythematous areas also seen[9,16,17]. The reported prevalence of ulceration in patients with SRUS was 57 per cent in one large series[9], with polypoid lesions in 25 per cent and patches of hyperaemic mucosa in 18 per cent. Lesions are multiple in 30 per cent of cases[3]. The lesion or lesions are most often found on the anterior or anterolateral wall of the rectum, typically between 5 and 10 cm from the anal margin and centred on a rectal fold.

Histology

A biopsy should always be taken. The histological features of SRUS are well documented[3,18,19]. There is a thickening of the mucosa with elongation and distortion of the glands, particularly at their bases. The glands can be displaced into the submucosa and this has been related to superficial bleeding[4]. The lamina propria is oedematous and contains a variable proliferation of fibroblasts. There is thickening of the muscularis mucosae and extension of the smooth muscle fibres from the muscularis mucosae, vertically upwards between the crypts (*Fig. 1*). Paradoxically, there is often no ductal ulceration, although there may be erosion of the surface epithelium, accompanied by fibrinous exudate and engorgement of capillaries with blood in the superficial lamina propria but no significant inflammatory cell infiltrate. Features which SRUS or mucosal prolapse share with ischaemic colitis are degeneration of the epithelium of the upper parts of the crypts, surface erosion, engorgement of superficial capillaries and a lack of inflammatory cells. Excess collagen deposition is observed in SRUS and in ischaemic colitis, although in the former the deposition seems to be more diffuse than the focal deposition found in the latter[20]. A 'transitional mucosa' pattern is frequently seen in chronic SRUS and is held to be a regenerative phenomenon in response to chronic ischaemia[21]. Ischaemic ulcers may appear grossly similar to adenocarcinoma[22], an important differential diagnosis of SRUS.

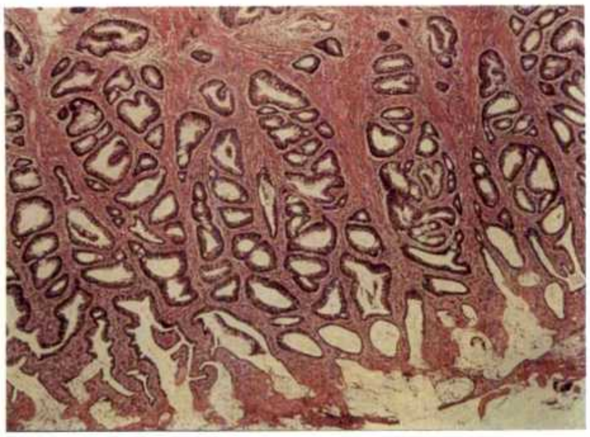

Fig. 1 Section of mucosa from a solitary rectal ulcer of the rectum, showing extension of muscle and fibrous tissue between the mucosal glands. The latter are hyperplastic, elongated and distorted. There is surface erosion. (Haematoxylin and eosin stain, original magnification × 15)

The fibrous replacement of the lamina propria and thickening of the muscularis mucosa are not unique to SRUS, and have also been documented in patients with rectal mucosal or full-thickness prolapse[14,23]. Operative full-thickness specimens from patients with the syndrome may show decussation and thickening of the two rectal muscle layers, nodular induration of the inner circular layer and grouping of the outer longitudinal layer[23]; these findings are unique to SRUS and are not seen in patients with isolated rectal prolapse.

The histological differential diagnosis of the syndrome includes inflammatory bowel disease and pseudomembranous colitis. Routine histological techniques suffice on most occasions[24] but in equivocal cases special stains may be employed. Diffuse excess collagen deposition is characteristic of SRUS and is a valuable method of differentiating it from inflammatory bowel disease[25]. Mucin staining patterns may also be used to distinguish this syndrome from other non-malignant conditions, with sialomucin present in all cases and sulphomucin present in most[26,27].

Radiological investigations

The diagnosis is made predominantly on the basis of symptoms, endoscopic appearance and histology. Radiological and physiological investigations are of limited value. However, characteristic radiological appearances have been described and these investigations have helped to define the aetiology of the condition.

Ultrasonography

Characteristic findings on both transrectal[28] and endoanal ultrasonography[29] have been described. The former reveals thickening of the muscularis propria and a lack of distinction between the mucosa and the muscularis propria. The lack of relaxation of the puborectalis during straining may also be seen. Although not a universal finding, marked thickening of the internal sphincter is the most striking feature of endoanal ultrasonography[29] (*Fig. 2*). This is most likely to be due to repeated trauma but an associated primary abnormality cannot be excluded. There is often an associated thickening of the external sphincter and the submucosa, the latter sometimes also losing its homogeneous appearance.

Defaecating proctography

Defaecography may be helpful in defining the underlying disorder in SRUS[30]. In a study of 53 patients with

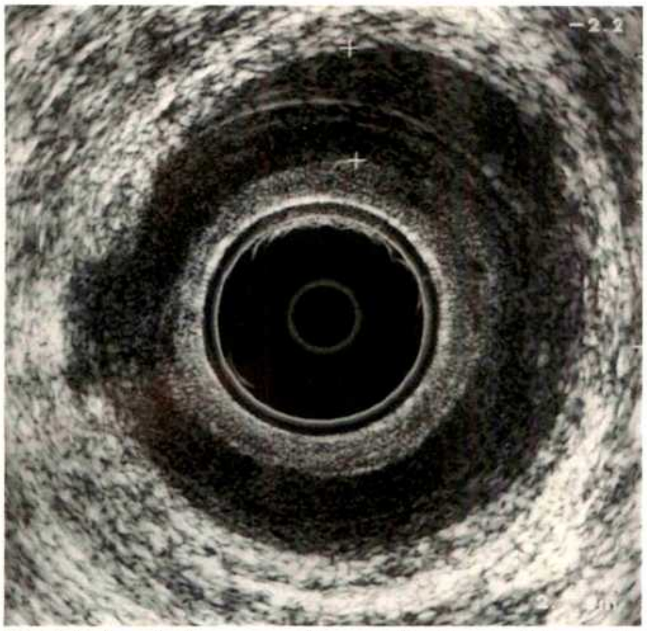

Fig. 2 Endoanal ultrasonographic scan of a 45-year-old man with solitary rectal ulcer syndrome. The internal anal sphincter is markedly thickened (7 mm). The image was taken using a 10-MHz probe

histologically proven SRUS, 40 were found to have unequivocal abnormalities on defaecation proctography compared with two of 20 age- and sex-matched controls. Internal or external rectal prolapse has been reported in 68 per cent of cases[31] and evacuation was also delayed or incomplete. A study using evacuation proctography before and after rectopexy showed almost invariable correction of the prolapse and alteration of rectal configuration at rest, but failed to identify any preoperative features which could be used to predict clinical outcome[32]. The presence of prolonged evacuation time after surgery correlated with a poor symptomatic outcome.

Barium enema

Barium enema is not a reliable test in the diagnosis of SRUS[33]. Nodularity of the rectal mucosa, thickening of the rectal folds, stricture formation, polypoid lesions and ulceration may be seen but cannot always be differentiated radiologically from the features of other more sinister conditions[34–37]. Barium enema has been reported to be normal in 40–50 per cent of cases[30,38].

Anorectal physiological studies

Physiological studies have been performed in patients with SRUS, but the results are variable and the tests do not contribute to making the diagnosis or to predicting therapeutic response. Keighley and Shouler[39] reported normal maximum resting and squeeze pressures on manometry, but others have reported reduced pressures[40,41]. These inconsistencies can be explained at least partly by taking into account the presence or absence of external rectal prolapse. The maximum resting pressure is reduced when the ulceration is associated with external prolapse[42]. Raised anal canal electrosensory thresholds[42,43] and raised anal canal and rectal electrosensory thresholds[42] have been reported and may relate to the effect of trauma on nerve function, to tissue disruption, or may be part of the primary pathology. The rectal distension threshold is often reduced, which may reflect a reduction in rectal compliance[39,40]. The reported high rectal voiding pressure is likely to relate to excessive straining[10]. There is general agreement on a high incidence of rectoanal inco-ordination, excessive perineal descent and pudendal neuropathy in patients with solitary rectal ulcer[44–46].

Pathogenesis

The cause of SRUS is unknown. Physiological[42] and histopathological[23] studies suggest a spectrum of disease, raising the possibility of a variety of causes in different patients. In clinical practice there is a subgroup of patients who strain excessively at stool, while in others such a behavioural disorder is not clinically apparent. In some patients ulceration occurs as part of overt external prolapse.

It is generally agreed that occult or overt rectal prolapse and paradoxical contraction of the pelvic floor muscles are among the factors involved in the development of SRUS. Opposing forces on the rectal mucosa have been described[47], with the downward force of defaecation being opposed by the paradoxical contraction of the pelvic floor. The rectal pressures required to achieve voiding in the face of external sphincter contraction are high, which may predispose to ischaemia and resulting ulceration[48]. The prolapsed mucosa may also become directly traumatized against the closed anal canal[10] or there may be shearing forces resulting in trauma to the bowel wall.

Puborectalis contraction during straining is not a universal finding in patients with SRUS, the incidence varying from 50 to 77 per cent[4,43,44,49–51]. The association between SRUS and rectal prolapse is also not entirely clear[15,42,52]. Some authors suggest that prolapse and ulceration are different stages of the same pathological process[40] while others suggest that the two conditions are of differing aetiologies[42]. The fact that the two coexist in many patients makes this distinction more difficult. The data regarding the incidence of rectal prolapse (either mucosal or full rectal) in patients with the syndrome vary from 13 per cent[1] to 94 per cent[10], with non-surgical series having fewer patients with demonstrable prolapse than surgical series. In one surgical series, rectal prolapse (internal in 12 and external in seven) was confirmed by evacuation proctography in 19 of 23 patients with SRUS before rectopexy[32]. Although surgery cured prolapse in all but one of them, there was no correlation between cure of prolapse and the symptomatic outcome of surgery[32], suggesting that prolapse may be associated rather than always causative. Magnetic resonance imaging combined with evacuation proctography may shed further light on the relationship between rectal wall movement and clinical findings.

Du Boulay and colleagues[53] have drawn attention to the association of the histological appearances of the mucosa in SRUS with those seen at sites of mucosal prolapse and have proposed that an important factor in pathogenesis is prolapse of rectal mucosa alone, as opposed to prolapse of the rectum as a whole. They suggested that the alternative term 'mucosal prolapse syndrome' be used for SRUS. Similar histological features are seen at any site of mucosal prolapse. Inflammatory cloacogenic polyp[54–56], a lesion found when rectal mucosa prolapses through the anus, sometimes in association with haemorrhoids, has almost identical histological features, as does inflammatory cap polyp[57] and inflammatory myoglandular polyp[58]. These last two lesions are the result of chronic prolapse of redundant mucosal folds in the colon, particularly the left colon. Similar histological features also occur at the site of prolapsing colonic and ileal mucosa at colostomy and ileostomy sites[59], and also occasionally in the redundant mucosal folds of sigmoid diverticular disease[60,61].

As mucosal prolapse shares several histological features with ischaemic colitis, it has been assumed that ischaemia is a factor in SRUS. The mucosa at the apex of a prolapsing fold may become ischaemic because of small blood vessel trauma. The possible role of ischaemia in the pathogenesis of SRUS is further highlighted by the association between suppositories of ergotamine (an α-adrenoreceptor agonist with potent vasoconstrictor action) and development of the syndrome[62,63]. Solitary rectal ulcer has also been reported following radiotherapy[64].

Direct trauma from rectal digitation has been suggested as a cause of the syndrome[65,66]. The reported incidence of digitation varies from series to series and in one report was said to be 100 per cent[65]. Many patients who rectally digitate over a number of years do not have any evidence of SRUS and equally there have been cases of SRUS described, particularly in children, in which direct trauma has been excluded[67–69]. The SRUS lesions are often located beyond the reach of a finger, making intrarectal prolapse or insertion of an instrument necessary to link the lesion to direct trauma. There is conflicting evidence as to whether anal intercourse is associated with SRUS[39,70]. In some patients, however, especially some with low rectal ulceration, direct trauma from a finger or other object can be identified as a cause.

Psychological problems associated with the syndrome have been explored only superficially. The only formal documentation is in a paper published in 1969[3] which suggested a 12 per cent incidence of mental abnormality, but this was only very crudely assessed. A disturbance of toileting behaviour, as an expression of psychological problems, appears to be an important pathogenic factor in some patients. Improvement in symptoms with behavioural treatment directed towards defaecation behaviour (biofeedback) supports this being an important pathogenic factor.

One prospective study has raised the possibility that SRUS is part of a systemic disease[12]. Of 22 patients with solitary rectal ulcer, four had oral ulceration, one erythema nodosum, six radiological evidence of sacroiliitis and four were human leucocyte antigen B27 positive. No corroborative studies have been published and none of the SRUS histological findings are characteristic of a vasculitis.

Treatment

There is no specific cure for SRUS. Symptoms may be improved by treatment but it is uncommon to achieve endoscopic and histological normality[4].

Conservative treatment

Local treatment. Application of local agents to the area of ulceration fails to address the underlying defaecatory disorder and is usually unsuccessful. Topical steroids and sulphasalazine enemas are not effective[9,11,71]. In a small open study, six patients were treated with sucralfate enemas (2 g twice daily for 3–6 weeks)[72,73]. Symptomatic improvement and macroscopic healing occurred in all patients although histological changes persisted[73].

Human fibrin sealant has been applied locally to the rectal ulcer and may provide a useful form of topical treatment. It stimulates fibroblast and vascular proliferation, leading to tissue regeneration. In one study all six patients treated with human fibrin sealant together with fibre and correction of straining had healing at 14 days; the ulcers remained healed at 1-year follow-up[74]. A control group treated with fibre and correction of straining alone had no healing at 14 days although half had healed by 1 year.

Fibre. Although dietary treatment has been recommended[35] there is little evidence to support this treatment. The response rate to bulking agents or dietary fibre is reported to range from 19 to 70 per cent, and patients with an associated prolapse seem to benefit least from this intervention alone[1,9]. In most studies the use of fibre has been combined with an attempt to discourage the patient from straining at defaecation[43,75]. In combination with habit training to reduce straining, 14 of 21 patients reported symptomatic improvement, and sigmoidoscopic disappearance of the ulcer occurred in eight[75]. These results are only achieved after months of meticulous therapy. A report of treatment with fibre and encouragement to stop digital rectal evacuation appeared to favour cessation of repeated trauma as the main factor in healing the ulcer in six of eight patients in another series[65].

Biofeedback behavioural retraining. In clinical practice some patients with SRUS appear to have a dominant behavioural disorder with excessive straining, while in others there is no history of straining. Encouraging results from the use of behavioural therapies for defaecation disorders have led to studies exploring whether some patients with SRUS might benefit from biofeedback retraining. Biofeedback has been used both as the sole therapy for solitary rectal ulcer and as a adjunct to surgical therapy. Binnie *et al.*[76] detailed 17 patients treated with a combined approach of surgery and biofeedback before or immediately after surgery. A comparison group of 14 patients treated conservatively or with surgery alone had a higher recurrence rate. In a study from Eigenmann and colleagues[77], two children were successfully treated for solitary rectal ulcer using biofeedback retraining.

There are only two reports of the use of biofeedback as the sole therapy for SRUS in adults[42,78]. In the first, only patients with demonstrable paradoxical puborectalis contraction were selected for this therapy and the follow-up time was less than 6 months in all cases[42]. The seven patients reported less straining, easier defaecation, and the cessation of bleeding and passage of mucus after treatment. In the second report, 13 consecutive patients were evaluated prospectively without restrictive criteria for inclusion in the biofeedback programme[78]. Five had failed previous surgical therapy. After a median follow-up of 9 months four patients were asymptomatic and four felt improved. Seven of the 13 patients stopped straining and only four remained on laxatives after treatment. The median number of visits to the toilet per day decreased from six before therapy to three after therapy and the median time spent in the toilet per visit decreased from 30 to 10 min. Three patients were able to maintain employment before treatment compared with eight after therapy. The ulceration did not heal completely in any of the nine patients examined after treatment, but it improved in four. Biofeedback for these patients included correction of pelvic floor defaecatory behaviour, regulation of toileting habits, encouragement to stop laxatives, suppositories and enemas, and an attempt to address any psychological factors which may have been relevant.

Surgical treatment

The least invasive operative procedures are suturing or local excision of the area affected by SRUS[79,80]. Excision of the ulcer using a neodymium yttrium–aluminium–garnet laser has been documented recently in 14 ulcerated patients[81]. Thirteen reported lasting symptom relief, but patients with rectal prolapse were excluded in this study. These local approaches fail to address the possible underlying aetiology of the condition and so the long-term benefit is uncertain.

The association of straining with SRUS suggests that any operation predisposing to constipation should be used only after due consideration. Rectopexy is certainly one such operation[6] and most reports have concentrated on short-term results alone. The best results have been reported after combined posterior and anterior approaches. Rectangles of Marlex (CR Bard, Billerica, Massachusetts, USA) mesh are sutured to the posterior and the anterior rectal wall, the latter supporting the area most commonly affected by the internal prolapse and ulceration. Twelve of 14 patients were improved in the first study using this technique but two of the 12 developed severe postoperative constipation[82].

A suggested modification is an additional anterior prolapsectomy to deal with the anterior mucosal prolapse[83]; symptomatic cure has been reported to be 80 per cent with symptoms abating within 1–2 months of the operation.

The long-term results of surgery have recently been addressed in 66 patients who had 72 procedures over a 10-year period, including rectopexy, Delorme's procedure and resection[84]. At interview, of the patients who had had a rectopexy 18 per cent had complete resolution of symptoms, 36 per cent had marked improvement, 9 per cent had only an initial improvement and 36 per cent had no improvement or felt worse after the operation. No patient had a complete resolution of symptoms after a Delorme's procedure but 56 per cent were greatly improved, 11 per cent had only initial improvement and 33 per cent were unchanged or worse. Resection with coloanal anastomosis or anterior resection improved only one of five patients. Overall, 52 per cent of patients who did not have a stoma were improved after surgery.

There are few other surgical reports in the literature. In a series reported by Keighley and Shouler[39] 14 patients with SRUS underwent abdominal rectopexy. There was a 50 per cent rate of macroscopic healing of the ulcer. Patients with rectal prolapse seemed to fare better after abdominal rectopexy than those without rectal prolapse. Of the eight patients with no associated prolapse only two had ulcer healing. In a further series[1] 27 patients had undergone 31 procedures; 14 procedures were performed on patients without prolapse and 17 in those with prolapse. There was an overall symptomatic improvement in 20 of 31 procedures. Median follow-up was 25 months with seven of ten patients having symptomatic improvement after rectopexy, five of ten after resection and six of nine after a 'local procedure'.

Resection may be used in conjunction with rectopexy in an attempt to decrease the incidence of postoperative constipation[85], or can be performed as the primary operation to remove the affected segment. In a recent study of resection and coloanal anastomosis for benign rectal lesions two patients with SRUS had poor results, both requiring a colostomy[86]. For some patients a stoma, either temporary diverting or permanent, is required[87]. Many, however, continue to experience functional symptoms.

Complications of solitary rectal ulcer syndrome

SRUS is a benign condition. Rarely it is associated with massive rectal bleeding which may then dictate the choice of operation. Some patients have been treated successfully with sclerotherapy or circumferential suturing[88]. However, in some cases local therapy is not successful, and it may be necessary to proceed to an anterior resection[89]. The condition may also be complicated by rectal stricture.

Discussion

SRUS is a rare disorder with characteristic clinical and investigative findings. The pathogenesis is likely to vary in different patients. Behavioural techniques directed towards defaecatory habits help in a substantial proportion of patients and should now form the first line of treatment. However, the long-term results of such treatment are still not known. The most commonly performed operation, rectopexy, helps about 50 per cent of patients but it increases symptoms in some. Surgery has only a very minor role and should be reserved for those with intractable symptoms who have failed a concerted effort with behavioural therapy and have evidence of prolapse. Progress is likely to come from a greater understanding of the role played by psychological and neuromuscular factors in the pathogenesis of SRUS.

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Review

Influence of study design on reported mortality and morbidity rates after abdominal aortic aneurysm repair

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Background The mortality and morbidity rates of elective abdominal aortic aneurysm (AAA) surgery, as reported over the past 12 years, were graded and analysed by levels of evidence.

Methods Articles on elective AAA surgery published between 1985 and 1996 were retrieved and classified into five levels of evidence. Level 1 contains prospective studies and is subdivided into population-based (level 1a) and hospital-based (level 1b) studies. Level 2 includes retrospective studies, subdivided into population-based studies (level 2a), hospital-based studies (level 2b) and hospital-based studies concerning a specified group of selected patients (level 2c). Operative mortality and systemic and local/vascular complication rates with 95 per cent confidence intervals were calculated for each level of evidence.

Results Seventy-two articles describing a total of 37 654 patients could be included: two level 1a studies (692 patients), nine level 1b studies (1677 patients), 13 level 2a studies (21 409 patients), 32 level 2b studies (12 019 patients) and 16 level 2c studies (1857 patients). The mean 30-day mortality rates of the two population-based levels were similar: 8·2 (95 per cent confidence interval 6·4–10·6) per cent for the prospective (1a) and 7·4 (7·0–7·7) per cent for the retrospective (2a) series. These figures were significantly higher than the remarkably similar hospital-based mortality rates: 3·8 (3·0–4·8) per cent for the prospective (1b), 3·8 (3·5–4·2) per cent for the retrospective (2b) and 3·5 (2·8–4·4) per cent for selected patient group (2c) studies. The most frequent complication was of cardiac origin. In the population-based series the cardiac complication rates were 10·6 (8·5–13·2) and 11·1 (9·1–13·6) per cent for levels 1a and 2a respectively. This compared well with 12·0 (10·5–13·9) per cent for the prospective hospital-based series (level 1b). The cardiac complication rates in the retrospective hospital-based studies were significantly lower: 8·9 (8·4–9·5) and 6·1 (4·9–7·6) per cent for levels 2b and 2c respectively.

Conclusion There is a clear and consistent disagreement in reported mortality rates between hospital-based and population-based studies of elective surgery for AAA. Prospective studies give the best documentation of postoperative morbidity.

After five relatively quiet decades of abdominal aortic aneurysm (AAA) repair, we are now witnessing the turbulent evolution of minimally invasive techniques[1]. Currently, before the long-term results of any endovascular AAA device can be evaluated, the marketing of the next generation of the device renders the evaluation of the previous one obsolete[2–4].

More than ever, reliable data on operative mortality and morbidity rates of conventional AAA repair are needed to allow meaningful comparison with the endovascular results. Unfortunately, the literature reveals a large variation in reported results of AAA surgery as a consequence of the different types of study design used, i.e. prospective *versus* retrospective and hospital-based *versus* population-based. Despite the multitude of studies conducted on the outcome of elective AAA surgery, to the authors' knowledge, no attempt has so far been made to classify these results by study design. The aim of the present study is to review a 12-year period of publications on mortality and morbidity rates associated with elective AAA repair and to compare outcomes using a level of evidence classification system designed for this purpose.

Materials and methods

Medline and *Current Contents* were used to retrieve articles published on mortality and morbidity rates associated with elective AAA surgery from January 1985 to December 1996. Studies concerning suprarenal or ruptured aneurysms or emergency repair were excluded from this review. Also excluded were articles on aortic reconstruction in which results were not recorded separately for AAA and other concurrent diseases studied simultaneously (e.g. aortoiliac occlusive disease, claudication and rest pain).

To make meaningful comparisons between different types of studies (prospective *versus* retrospective and population based *versus* hospital based), the classification system of levels of evidence as originally proposed by Cook *et al.*[5] was adapted. *Table 1* shows the original version as applied to studies on antithrombotic agents. The focus of the present review concerned studies without control subjects, so a further breakdown of level V of the Cook classification (case series without controls) was necessary. This was done by taking into account the study design (prospective or retrospective) and the population studied. A study was designated population based if patients were identified by means of a national or regional

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registry. All other reports, whether single-centre or multicentre in nature were evaluated as hospital-based studies.

Table 2 lists the levels of evidence applied in this review. Level 1 contains prospective studies, and is further subdivided into population-based (level 1a) and hospital-based (level 1b) studies. Retrospective studies are grouped in level 2 and this level contains three subgroups: population-based studies (level 2a), hospital-based studies (level 2b) and hospital-based studies concerning a selected group of high-risk patients (level 2c). In this last subclass, the patient population included most frequently comprises the elderly but groups of patients with diabetes mellitus, coronary artery disease, renal failure, hypothermia or concurrent gastrointestinal surgery are also involved.

Postoperative complications, as derived from the original publications, were classified according to the revised version Suggested Standards recommended by the Ad Hoc Committee on Reporting Standards of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery[6]. Because few studies reported on all complication categories of interest, each complication as presented in *Table 3* was analysed separately. For instance, cardiac morbidity was analysed using only articles that documented cardiac complications. The summed patient numbers from the relevant studies yielded the number at risk of this complication. For all complication categories, the number of patients at risk divided by the total patient number was defined as the proportion at risk. These proportions were calculated for each level of evidence.

Table 1 Levels of evidence described by Cook *et al.*[5]

Level of evidence	Definition
Level I	Randomized trials with low false-positive (α) and low false-negative (β) errors
Level II	Randomized trials with high false-positive and high false-negative errors
Level III	Non-randomized concurrent cohort studies
Level IV	Non-randomized historical cohort studies
Level V	Case series without control subjects

Table 2 Modified levels of evidence

Level of evidence	Definition
Level 1a	Prospective population-based studies
Level 1b	Prospective hospital-based studies
Level 2a	Retrospective population-based studies
Level 2b	Retrospective hospital-based studies
Level 2c	Retrospective hospital-based studies concerning selected groups

Table 3 Postoperative complications after abdominal aortic aneurysm repair[6]

- Systemic
  - Cardiac
  - Cerebral (transient ischaemic attack or stroke)
  - Pulmonary
  - Renal
  - Gastrointestinal
- Local/vascular
  - Limb ischaemia
  - Intraoperative and/or postoperative haemorrhage
  - Wound infection
  - Graft infection
  - Graft thrombosis
  - Wound dehiscence

Mortality and postoperative morbidity was defined as 30-day or in-hospital death or complications. The original data published were recalculated if necessary to comply with this definition. Mean mortality and morbidity rates and 95 per cent confidence intervals were calculated for each level of evidence (χ^2 test).

Results

A total of 72 articles describing conventional, elective, infrarenal AAA surgery in a total of 37 654 patients could be included[7–78]. Distribution over the five levels of evidence is given in *Table 4*.

The mean mortality rates of the five types of study design are depicted in *Fig. 1*. In the population-based studies mortality rates were similar: 8·2 (95 per cent confidence interval 6·4–10·6) per cent for the prospective (1a) and 7·4 (7·0–7·7) per cent for the retrospective (2a) series. These figures were significantly higher than the remarkably similar hospital-based mortality rates: 3·8 (3·0–4·8) per cent for the prospective (1b), 3·8 (3·5–4·2) per cent for the retrospective (2b) and 3·5 (2·8–4·4) per

Table 4 Studies and patients included

	Level				
	1a	1b	2a	2b	2c
No. of studies	2	9	13	32	16
References	7, 8	9–17	18–30	31–62	63–78
No. of patients	692	1677	21 409	12 019	1857

Level 1a, prospective population-based studies; level 1b, prospective hospital-based studies; level 2a, retrospective population-based studies; level 2b, retrospective hospital-based studies; level 2c, retrospective hospital-based studies concerning selected groups

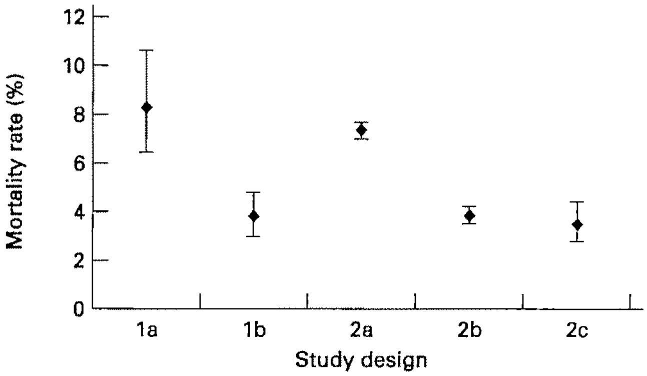

Fig. 1 Mean mortality rates (with 95 per cent confidence intervals) of the five levels of evidence. Level 1a, prospective population-based studies; level 1b, prospecitve hospital-based studies; level 2a, retrospective population-based studies; level 2b, retrospective hostpital-based studies; level 2c, retrospective hospital-based studies concerning selected groups

cent for selected patient group (2c) studies ($P < 0{\cdot}05$). The reporting rate of death was 100 per cent in all levels.

The reporting rates for systemic complications are depicted in *Table 5* and for local/vascular complications in *Table 6*. For level 2a, the reporting rate of morbidity was less than 5 per cent for all complications. For the other four levels, the reporting rate of cardiac complications was above 70 per cent. Systemic complications had high reporting rates (46–96 per cent) in the prospective series (level 1a and 1b), but only the prospective hospital-based studies (level 1b) attained notable reporting rates for the local/vascular complications (37–58 per cent). Also listed

Table 5 Systemic complications

	Level 1a (*n* = 692)	Level 1b (*n* = 1677)	Level 2a (*n* = 21 409)	Level 2b (*n* = 12 019)	Level 2c (*n* = 1857)
Cardiac					
No. at risk	661	1386	749	9661	1291
Reporting rate (%)	96	83	3	80	70
Complicaton rate (%)	10·6 (8·5–13·2)	12·0 (10·5–13·9)	11·1 (9·1–13·6)	8·9 (8·4–9·5)	6·1 (4·9–7·6)
Cerebral					
No. at risk	661	776	692	1742	1004
Reporting rate (%)	96	46	3	14	54
Complication rate (%)	1·4 (0·7–2·6)	0·6 (0·3–1·5)	1·3 (0·7–2·5)	0·7 (0·4–1·3)	0·9 (0·5–1·7)
Pulmonary					
No. at risk	661	1220	488	5619	465
Reporting rate (%)	96	73	2	47	25
Complication rate (%)	5·3 (3·8–7·3)	9·8 (8·3–11·6)	10·5 (8·0–13·5)	3·5 (3·1–4·0)	5·6 (3·8–8·1)
Renal					
No. at risk	661	1220	431	2548	1016
Reporting rate (%)	96	73	2	21	55
Complication rate (%)	7·0 (5·3–9·2)	4·8 (3·8–6·2)	9·0 (6·7–12·1)	3·6 (2·9–4·4)	3·1 (2·2–4·3)
Gastrointestinal					
No. at risk	661	1286	389	4400	494
Reporting rate (%)	96	77	2	37	27
Complication rate (%)	0·2 (0·0–0·9)	13·0 (11·3–14·9)	2·1 (1·0–4·0)	1·7 (1·4–2·2)	3·0 (1·8–4·9)

Values in parentheses are 95 per cent confidence intervals. Level 1a, prospective population-based studies; level 1b, prospective hospital-based studies; level 2a, retrospective population-based studies; level 2b, retrospective hospital-based studies; level 2c, retrospective hospital-based studies concerning selected groups

Table 6 Local vascular complications

	Level 1a (*n* = 692)	Level 1b (*n* = 1677)	Level 2a (*n* = 21 409)	Level 2b (*n* = 12 019)	Level 2c (*n* = 1857)
Limb ischaemia					
No. at risk	661	621	156	1039	123
Reporting rate (%)	96	37	1	9	7
Complicaton rate (%)	0·5 (0·2–1·3)	5·8 (4·2–7·9)	1·9 (0·7–5·5)	3·7 (2·7–5·0)	2·4 (0·8–6·9)
Haemorrhage					
No. at risk	661	776	431	4175	436
Reporting rate (%)	96	46	2	35	23
Complication rate (%)	0·2 (0·0–0·9)	6·2 (4·7–8·1)	1·6 (0·8–3·3)	0·7 (0·5–1·0)	1·8 (0·9–3·6)
Wound infection					
No. at risk	0	921	332	1241	691
Reporting rate (%)	0	55	2	10	37
Complication rate (%)	—	1·5 (0·9–2·5)	2·1 (1·0–4·3)	4·1 (3·1–5·4)	0·4 (0·1–1·3)
Graft infection					
No. at risk	0	921	332	0	0
Reporting rate (%)	0	55	2	0	0
Complication rate (%)	—	0·3 (0·1–1·0)	0·6 (0·2–2·2)	—	—
Thrombosis					
No. at risk	0	921	431	3435	123
Reporting rate (%)	0	55	2	29	7
Complication rate (%)	—	1·1 (0·6–2·0)	2·1 (1·1–3·9)	0·5 (0·3–0·8)	3·3 (1·3–8·1)
Dehiscence					
No. at risk	0	965	0	237	227
Reporting rate (%)	0	58	0	2	12
Complication rate (%)	—	0·6 (0·3–1·3)	—	0·8 (0·2–3·0)	0·9 (0·2–3·2)

Values in parentheses are 95 per cent confidence intervals. Level 1a, prospective population-based studies; level 1b, prospective hospital-based studies; level 2a, retrospective population-based studies; level 2b, retrospective hospital-based studies; level 2c, retrospective hospital-based studies concerning selected groups in *Tables 5* and *6* are the rates of systemic and local/vascular complications respectively. Cardiac complications were most frequently encountered.

In the population-based series the cardiac complication rate was 10·6 (8·5–13·2) and 11·1 (9·1–13·6) per cent for levels 1a and 2a respectively. This compared well with 12·0 (10·5–13·9) per cent for the prospective hospital-based series (level 1b). The cardiac complication rates in the retrospective hospital-based studies were significantly lower: 8·9 (8·4–9·5) and 6·1 (4·9–7·6) per cent for levels 2b and 2c respectively.

Discussion

Despite the availability of reporting standards for vascular surgery before the decade of the present literature review, only a few articles appear to have followed the guidelines proposed by the ad hoc committee of the Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery[79]. The attempts made thus far to summarize operative mortality and morbidity rates from the literature involved clustering of data irrespective of the various types of study design[80–83]. The present authors have demonstrated that the vast majority of studies reporting on AAA surgery describe only a specific selection of complications. As such, the total number of patients described in this clustered data is not equal to the actual number of patients for which the presence or absence of a certain complication was documented. This aggregated analysis leads to an underestimation of the true morbidity rates. In the present study morbidity was analysed relative to the numbers at risk for each complication and data were grouped according to study design. This resulted in strikingly similar mortality and morbidity rates in the levels of evidence examined.

Study design

Typically, mortality rates in prospective population-based studies (level 1a) are relatively high, representing results in a non-selected population. Because of their prospective nature, these studies also have the highest proportions at risk for significant systemic complications. The more specific complications like graft infection or graft thrombosis are usually not documented. Studies of this type are scarce.

Most randomized trials fall into level 1b (prospective hospital-based studies). These studies are characterized by reporting on a large number of complication categories but, on the other hand, they involve multiple inclusion and exclusion criteria and also a selection of complications relevant to the trial. In addition, this type of study is prone to publication bias[84].

Retrospective population-based studies (level 2a) contain massive patient numbers resulting in rather small confidence limits for the complication rates. Typically these studies use government or health care registries. These registries are usually quite accurate in documenting death, but they are unreliable with respect to morbidity. It should also be taken into consideration that in most countries these registries distinguish only between ruptured and non-ruptured AAA. As such, the results of the acutely treated symptomatic, but non-ruptured, AAA are combined with the outcome of purely elective AAA repair. The population-based studies cannot therefore be compared with the hospital-based studies.

However, with their large patient numbers these reports can be considered to represent the gold standard for operative mortality data. The fact that the mortality rates of these retrospective population-based studies are very similar to those of the prospective population-based studies demonstrates the reliability of the registries used. The dissimilarity between mortality and morbidity rates of the two population-based studies (level 1a and 2a), on one hand, and the hospital-based studies (level 1b and 2b/c), on the other, puts the latter into perspective. But as stated above, neither study type can be identified as overestimating or underestimating mortality and morbidity rates.

Level 2b reports (retrospective hospital-based studies) typically include single-centre/author experience and so are not only subject to publication bias but also to the many biases related to observational studies[85]. Although these studies lack the specific inclusion and exclusion criteria of level 2a, their retrospective nature suggests that most complication rates are underestimated.

Level 2c (retrospective hospital-based studies concerning selected groups) combines all the unfavourable aspects of the previous levels. While reporting mortality and morbidity rates of a specific group of patients (i.e. octogenarians or patients with pulmonary disease) these studies suffer from both publication and selection bias. In addition, their retrospective nature casts doubt on the completeness of the documentation. The mean mortality rate of 3·5 per cent in this group is comparable to that of the hospital-based studies. It is important to note, however, that five of the 16 studies[63,69,72,75,76] included in this level did not report any postoperative complications and reported only deaths. Four studies[68,70,74,78] documented one or two types of complications, and two studies[71,73] did not document morbidity for elective and emergency surgery separately. Therefore, it is difficult to make meaningful comparisons regarding morbidity with other levels, as it does not reflect the overall effect of elective surgery for AAA.

Mortality and morbidity rates

What is the mortality rate associated with elective conventional AAA repair? Clearly, there is no single answer to this question. The population-based figures indicate about 8 per cent but several authors have demonstrated that careful selection of patients can result in a mortality rate of less than 2 per cent. Morbidity rates vary too much to extract valid overall conclusions. Cardiac complications are the most frequent form of postoperative morbidity encountered after elective AAA repair in all levels except in level 1b. They comprise mostly myocardial infarction, dysrhythmia and congestive heart failure. It is, however, difficult to investigate which cardiac complication was most often observed because not all articles documented these problems in detail. One study that did record various types of cardiac complications separately was that of Johnston[11] which reported an occurrence of myocardial infarction of 5·2 per cent, of congestive heart failure of 8·9 per cent and of dysrhythmia of 10·5 per cent. Complication rates after long-term follow-up have been reported[86]. These results do not contradict the data used in the present review.

A final factor responsible for an increased variation in reported morbidity is the fact that study populations differ from one another with respect to risk factors such as age, pre-existing cardiac problems, chronic obstructive pulmonary disease and other vascular pathologies.

Conclusion

There is a clear and consistent disagreement in reported mortality rates between hospital-based and population-based studies of elective surgery for AAA. Prospective studies give the best documentation of postoperative morbidity. Categorizing studies using levels of evidence could provide a primary stratification for reports on elective AAA repair, permitting better interpretation and comparison of results than have hitherto been possible.

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Plasma concentration of cytokine antagonists in patients with infection following liver resection

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Background The interactions between endogenous cytokine antagonists, surgical injury and perioperative infection are poorly understood.

Methods Perioperative plasma concentrations of soluble tumour necrosis factor receptor p55 (STNFR p55), interleukin (IL) 1 receptor antagonist (IL-1ra) and IL-6 were measured by immunoassay in 29 consecutive patients undergoing liver resection.

Results Plasma concentrations of STNFR p55, IL-1ra and IL-6 showed a striking increase immediately after operation (day 0) and on postoperative day 1. STNFR p55 concentrations correlated significantly with operating time ($P < 0{\cdot}05$); IL-1ra levels with operating time, blood loss and weight of resected liver ($P < 0{\cdot}05$); and IL-6 concentrations with operating time and blood loss ($P < 0{\cdot}05$). Eight of the 29 subjects developed postoperative infections, of whom four had positive cultures of enteric organisms. Plasma STNFR p55 and IL-6 concentrations were significantly higher in the infected group than in the uninfected group ($P < 0{\cdot}05$). STNFR p55 and IL-6 concentrations on day 0 differentiated between the two groups with a diagnostic accuracy of 79 and 83 per cent respectively.

Conclusion These results suggest that STNFR p55, IL-1ra and IL-6 are produced during operation in response to surgical stress. This production of STNFR p55 and IL-6 may be enhanced further by intraoperative bacterial translocation. Measurement of plasma STNFR and IL-6 concentrations may predict the development of postoperative infectious complications.

Liver resection, especially for biliary tract cancers, is associated with a high morbidity rate[1,2] which has spurred attempts to reduce postoperative infectious complications.

The postoperative immune response is believed to be mediated by the proinflammatory cytokines interleukin (IL) 1 and tumour necrosis factor (TNF), and modulated by the naturally occurring specific antagonists of these cytokines[3]. Postoperative production of TNF and IL-1 has been investigated after major surgery including extensive liver resection[4–7]. In contrast, production of cytokine antagonists following liver resection has been little studied. Increased concentrations of soluble TNF receptor (STNFR) and IL-1 receptor antagonist (IL-1ra) have been reported in various pathological states, and are usually correlated with disease activity[8–10]. Furthermore, a recent report has concluded that increased serum concentrations of STNFR p55 after cardiac surgery allow early prediction of subsequent sepsis[11]. Finally, the cytokine IL-6 has anti-inflammatory properties in addition to inflammatory effects following injury[12]. The purpose of the present study was to investigate the role of cytokine antagonists in the pathophysiology of patients who develop postoperative infection following liver resection.

Patients and methods

Twenty-nine consecutive patients undergoing liver resection were studied (ten women, 19 men; age range 24 to 78 (median 64) years). They included nine patients with biliary tract cancer (bile duct cancer, five; gallbladder cancer, four); 14 patients with hepatic metastases (from colorectal cancer in ten, gastric cancer in two and breast cancer in two); and six patients with primary liver tumour (cholangiocarcinoma, three; hepatocellular carcinoma, one; hepatocellular adenoma, one; cavernous haemangioma, one). Liver resection performed in these patients included 12 extended right hepatectomies, nine right hepatectomies, two extended left hepatectomies, three left hepatectomies and three segmentectomies.

In all patients peripheral venous blood samples were collected before operation (baseline measurements), immediately after operation (day 0), and on days 1, 3, 5, 7 and 14 after operation. Samples were collected into Venoject tubes containing ethylenediamine tetra-acetic acid (Terumo, Tokyo, Japan). Plasma concentrations of STNFR p55, IL-1ra and IL-6 were measured. This protocol was approved by the hospital ethics committee. Informed consent was obtained from all patients studied.

Measurement of cytokine antagonists and interleukin 6

Plasma STNFR p55 concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Amersham International, Amersham, UK) using a monoclonal anti-STNFR p55 antibody for the solid phase and polyclonal anti-STNFR p55 antibodies for the liquid phase. Plasma IL-1ra concentrations also were determined using an ELISA kit (Amersham). Plasma IL-6 concentrations were determined by ELISA (R&D Systems, Minneapolis, Minnesota, USA) using a murine monoclonal antibody against IL-6 for the solid phase and polyclonal antibodies against IL-6 for the liquid phase.

Statistical analysis

Results are presented as mean(s.d.). The Mann–Whitney *U* test and the Wilcoxon signed rank test were used to analyse unpaired and paired samples respectively. Fisher's exact probability

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Table 1 Postoperative infections

Patient no.	Disease	Infection	Onset (days after operation)	Culture	Gut origin
1	Gallbladder cancer	Pneumonia	2	Positive	No
2	Bile duct cancer*	Wound infection	5	Positive	Yes
3	HCC	Pneumonia	3	Negative	
4	Metastasis from rectal cancer	Pneumonia	3	Positive	Yes
		Peritoneal abscess	3	Positive	Yes
5	Hepatocellular adenoma	Peritoneal abscess	10	Positive	No
6	Bile duct cancer*	Peritoneal abscess	5	Positive	No
7†	Bile duct cancer*	Pneumonia	4	Positive	No
		Peritoneal abscess	7	n.d.	
8	Gallbladder cancer*	Peritoneal abscess	10	Positive	Yes

*Patients with preoperative biliary obstruction. †Died from sepsis. HCC, hepatocellular carcinoma; n.d., not determined

method was used to assess the significance between proportions. Operative parameters such as operating time, blood loss, weight of resected liver and hepatic ischaemic time were correlated with plasma concentrations of cytokine antagonists and IL-6 using Spearman's correlation coefficient. P < 0·05 was considered statistically significant.

Results

Outcome

Eight of the 29 subjects developed postoperative infectious complications; these patients comprised the infected group. Clinical details of patients with postoperative infections are listed in *Table 1*. Of eight patients with infection, seven had positive cultures from the focus of infection and four had cultures positive for enteric bacteria. Of the 21 patients constituting the uninfected group, one developed heart failure due to myocardial infarction. Another patient in the uninfected group died from liver failure without infection. The other 19 uninfected patients recovered from surgery with no postoperative complications. Overall, ten of 29 patients suffered complications and two died.

Operative parameters

Operative parameters for the two groups of subjects are shown in *Table 2*. The infected group had significantly longer operating times and larger volumes of blood loss than the uninfected group. Resected liver weight and hepatic ischaemic time were not significantly different between the two groups.

Plasma concentrations of soluble tumour necrosis factor receptor p55

No significant difference was evident between infected and uninfected groups with respect to preoperative plasma STNFR p55 concentrations. In all patients partial hepatectomy resulted in a striking increase in plasma STNFR p55 concentrations on day 0 and day 1 after operation, followed by a rapid decline. The mean(s.d.) plasma STNFR p55 concentration was significantly higher in the infected group than in the uninfected group on day 0 and day 1 (day 0: 2·81(1·18) *versus* 1·74(0·76) ng/ml, P = 0·041; day 1: 2·44(1·73) *versus* 1·24(0·50) ng/ml, P = 0·017) (*Fig. 1a*). Respective cut-off values of 1·9 and 1·5 ng/ml for STNFR p55 on day 0 and day 1 resulted in a diagnostic accuracy of 79 per cent at each time point for separation of infected from uninfected patients.

Table 2 Clinical and operative profiles of all patients

	Infected group	Uninfected group	P
No. of patients	8	21	
Age (years)*	55·9(15·3)	61·0(13·6)	0·296†
Sex ratio (M:F)	6:2	13:8	0·675‡
Disease			
Primary liver tumour	2	4	
Metastatic tumour	1	13	
Biliary tract tumour	5	4	
Type of liver resection			
Extended right hepatectomy	4	8	
Right hepatectomy	2	7	
Extended left hepatectomy	0	2	
Left hepatectomy	1	2	
Segmentectomy	1	2	
Operative parameters*			
Operating time (min)	446(126)	321(117)	0·022†
Blood loss (g)	1896(1080)	874(797)	0·007†
Resected liver weight (g)	918(666)	597(248)	0·118†
Hepatic ischaemia time (min)	40(22)	31(19)	0·179†

*Values are mean(s.d.). †Mann–Whitney U test; ‡Fisher's exact probability method

Plasma concentrations of interleukin 1 receptor antagonist

In all patients partial hepatectomy resulted in a striking increase in plasma IL-1ra concentration immediately after operation with a subsequent rapid decline. Plasma IL-1ra concentrations did not differ significantly between the infected and uninfected groups throughout the study (*Fig. 1b*).

Plasma concentrations of interleukin 6

There was no significant difference between infected and uninfected groups in preoperative plasma IL-6 levels. In all patients partial hepatectomy resulted in a striking increase in plasma IL-6 concentration on day 0 and day 1 after operation, followed by a rapid decline. The mean(s.d.) plasma IL-6 level was significantly higher in the infected group than in the uninfected group on day 1 (508(335) *versus* 190(203) pg/ml; P = 0·045) (*Fig. 1c*). Cut-off values of 300 and 260 pg/ml for IL-6 on day 0 and day 1 resulted in respective diagnostic accuracies of 83 and 79 per cent in separating the infected and uninfected groups.

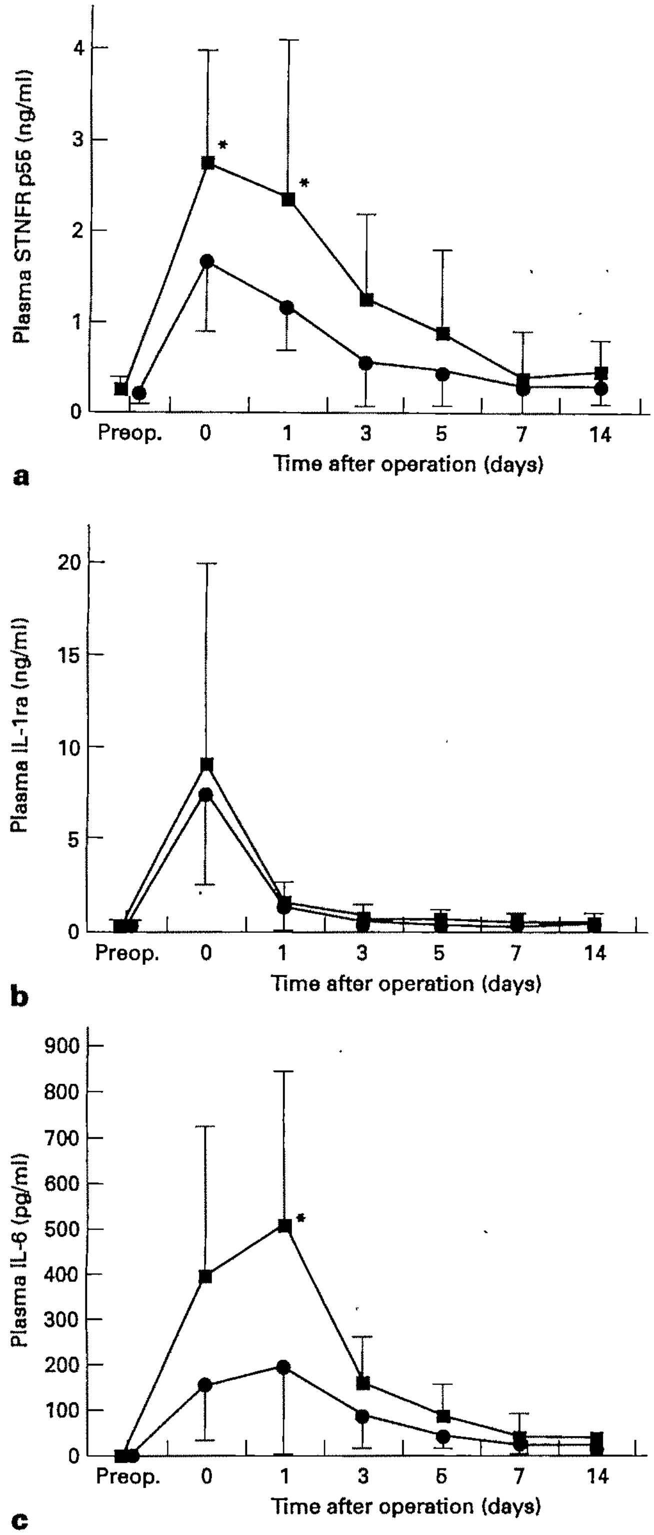

Fig. 1 Mean(s.d.) plasma concentrations of a soluble tumour necrosis factor receptor (STNFR) p55, b interleukin (IL) 1 receptor antagonist (IL-1ra) and c IL-6. ■, Patients with postoperative infectious complications; ●, patients without postoperative infection. $*P < 0\cdot05$ *versus* uninfected group (Mann–Whitney *U* test)

Correlation of operative parameters with plasma concentrations of cytokine antagonists and interleukin 6

Plasma concentrations of STNFR p55 on day 0 significantly correlated with operating time ($r_S = +0\cdot54$, $P = 0\cdot005$). Neither blood loss nor resected liver weight correlated with plasma STNFR p55 concentrations. Plasma concentrations of IL-1ra on day 0 correlated significantly with operating time ($r_S = +0\cdot38$, $P = 0\cdot045$), intraoperative blood loss ($r_S = +0\cdot44$, $P = 0\cdot020$) and resected liver weight ($r_S = +0\cdot51$, $P = 0\cdot007$). Plasma concentrations of IL-6 on day 0 correlated significantly with operating time ($r_S = +0\cdot53$, $P = 0\cdot005$) and intraoperative blood loss ($r_S = +0\cdot40$, $P = 0\cdot034$). Hepatic ischaemic time showed no correlation with plasma levels of cytokine antagonists or IL-6.

Discussion

TNF and IL-1, the primary proinflammatory cytokines[12], have been implicated in the pathogenesis of septic complications[13–17]. However, it is controversial whether TNF and IL-1 levels increase in the serum after major surgery[4–7]. Some reports have observed a significant increase in serum TNF-α and IL-1 levels in the perioperative period; these mean concentrations were less than 50 pg/ml for TNF-α[11] and about 15 pg/ml for IL-1[4]. In the present study, STNFR p55 and IL-1ra concentrations increased immediately after liver resection. At the concentrations attained in the present patients, STNFR p55 and IL-1ra would be expected to effectively neutralize circulating respective ligand effects *in vitro*[18–20]. However, the capacity of STNFR and IL-1ra to effectively neutralize their respective ligands in humans is not well established[21,22]. The fact that plasma STNFR p55 concentrations were significantly higher in the infected group suggests that the levels of this antagonist measured in the present study may not be sufficient to achieve full ligand antagonism under *in vivo* conditions. Timely administration of exogenous STNFR and IL-1ra might provide a therapeutic benefit in patients at high risk of sepsis[21,22].

STNFRs are released by activated neutrophils[23], mononuclear blood cells and fibroblasts[24], by shedding from cell membranes[23]. A recent report found that increased serum STNFR p55 concentrations on day 1 following cardiac surgery predicted subsequent sepsis and poor outcome, and that STNFR p75 was less predictive[11]. Furthermore, STNFR p75 concentrations measured after liver transplantation reportedly increase before the development of severe infection[25]. In the present study, increased plasma concentrations of STNFR p55 on day 0 or 1 predicted subsequent infectious complications.

Bacterial products such as formyl methionyl leucyl phenylalanine may be the primary inducers of STNFR release from neutrophils in patients with infection[23]. Major liver resection is reported to impair gut barrier function, resulting in increased translocation of enteric bacteria to mesenteric lymph nodes, viscera and the systemic circulation in rats[26]. Enteric bacteria were isolated from peritoneal fluid following major liver resection in humans[27]. Moreover, in the present study, enteric bacteria were isolated from the foci of infection. Therefore, intraoperative bacterial translocation from the bowel may be a major stimulus causing the increased plasma concentration of STNFR p55 and subsequent clinical infection. The present study also suggests that patients with biliary tract cancer are liable to infection. Patients at high risk of sepsis may require adequate preoperative preparation and postoperative intensive sepsis therapy. Furthermore, intraoperative contamination should be avoided.

Human monocytes produce IL-1β and IL-1ra proteins in similar quantities[28]. As monocytes mature to become macrophages, IL-1β production is downregulated and IL-1ra production is greatly enhanced[29]. Thus, tissue macrophages may be the major source of IL-1ra after surgery. In the present study, postoperative concentrations of plasma IL-1ra correlated significantly with operating time, intraoperative blood loss and resected liver weight. There was no significant difference in plasma IL-1ra concentrations between the infected and uninfected groups, suggesting that operative stress activated tissue macrophages including Kupffer cells and that IL-1ra concentrations simply reflect the severity of inflammation resulting from liver resection.

It has been reported that patients with postoperative complications have higher plasma levels of IL-6 than those without complications[4,30]. In the present study, postoperative concentrations of IL-6 also predicted postoperative infection. Intraoperative bacterial translocation leading to the postoperative infection, which is expected to enhance the production of STNFR p55, may also potentially upregulate IL-6 synthesis[12]. In the postoperative period, IL-6 can induce an earlier increase in the inflammatory response and also following late immunosuppression[31], thus promoting the development of postoperative infection. Soluble IL-6 receptor may be unable to neutralize its ligand effects[31]. Monoclonal antibodies directed at either IL-6 or its receptor might attenuate the inflammatory response and delayed host immunosupression[32].

In conclusion, the present study suggests that STNFR p55, IL-1ra and IL-6 are produced during operation in response to surgical stress, and that the production of STNFR p55 and IL-6 may be further enhanced by intraoperative bacterial translocation. In addition, plasma STNFR and IL-6 concentrations may predict the development of postoperative infectious complications.

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Amelioration of liver injury by ischaemic preconditioning

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Background Ischaemic preconditioning, i.e. preparatory brief ischaemia before subsequent long ischaemia, can effectively protect the heart from ischaemia–reperfusion injury in animals. The purpose of this study was to demonstrate the same phenomenon in the liver.

Methods Using warm ischaemia–reperfusion of 70 per cent of the liver followed by resection of the non-ischaemic portion in rats, livers with 10 min of ischaemic preconditioning, i.e. 10 min of warm ischaemia and reperfusion, were compared with those that had not been subjected to such a manoeuvre.

Results At 120 min after reperfusion following 40 min of warm ischaemia, the livers with 10 min of ischaemic preconditioning had a significantly lower mean(s.d.) serum alanine aminotransferase level (492(217) *versus* 1236(695) units/l; $P < 0{\cdot}005$) and lactic dehydrogenase level (7905(4002) *versus* 15 066(9201) units/l; $P < 0{\cdot}05$), as well as a higher bile output (0·12(0·03) *versus* 0·09(0·04) ml per g liver; $P < 0{\cdot}05$) and liver tissue adenosine 5′-triphosphate level (78(13) *versus* 61(11) per cent; $P < 0{\cdot}05$) than the control livers. The necrosis rate, histologically defined as the percentage of necrotic area in given liver sections, was reduced significantly by this manoeuvre (mean(s.d.) 1·3(1·3) *versus* 5·3(1·7) per cent; $P < 0{\cdot}05$).

Conclusion Ischaemic preconditioning exerts a protective effect on hepatic warm ischaemia–reperfusion injury. Such a manoeuvre may be useful for hepatic resection in the clinical setting.

Ischaemic preconditioning protects the canine heart from myocardial necrosis caused by long ischaemia[1]. For the myocardium, preconditioning by a single 5 min of ischaemia was as effective as by multiple intermittent ischaemia[2], while a single 2 min of ischaemia failed to exert any protective effect[3]. For the myocardium, the optimal interval between ischaemic preconditioning and subsequent long ischaemia has been reported to be 60 min[4]. The protective effect of ischaemic preconditioning on the myocardium has been proved in humans[5,6] and in animals[7–9]. To the authors' knowledge, however, little has been written about ischaemic preconditioning of the liver[10–12]. The purpose of this study was to clarify the protective effect of ischaemic preconditioning on ischaemia–reperfusion injury of the liver.

Materials and methods

Inbred male Wistar rats, weighing 220–300 g, were used for the experiment. The rats were fed on commercial pellets and water *ad libitum* in specific pathogen-free conditions. Each experiment was started at 09.00 hours to avoid the effect of circadian rhythm. The experimental design was reviewed and approved by the institution's Ethics Committee on Animal Experiments, and carried out following the Guideline for Animal Experiments at this university and the Law (No. 105) and Notification (No. 6) of the Japanese Government.

Operative procedure

All animals were anaesthetized with intraperitoneal pentobarbital 50 mg/kg. Laparotomy was carried out through a midline incision. Ligamentous attachments around the liver were divided. Ischaemia was induced in the median and left lateral hepatic lobes by clamping the corresponding hepatic arterial and portal venous branches *en masse* according to the method of Kawano *et al.*[13,14]. The blood flow to the other lobes was left intact. When the assigned period of warm ischaemia was completed, the clamp was removed and the inflow pedicles to the non-ischaemic lobes were resected after ligation of the corresponding pedicles *en masse* (*Fig. 1*). This technique abrogates the effect of splanchnic congestion caused by total occlusion of the portal vein during hepatic ischaemia[13–15]. The common bile duct was then

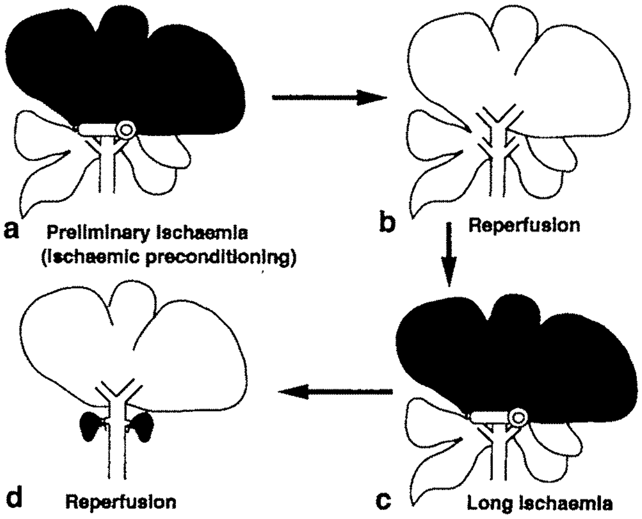

Fig. 1 Technique for hepatic pedicle clamping. a Ischaemic preconditioning was induced by clamping the corresponding hepatic arterial and portal venous branches *en masse*. b After a brief period of inflow occlusion of the liver, the clamp was released. c Long ischaemia was induced in the same manner. d After prolonged warm ischaemia, the clamp was removed and the non-ischaemic lobes were resected after ligation of the corresponding hepatic pedicles *en masse*

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cannulated and bile output from the remnant ischaemic liver, i.e. the median and left lateral lobes, was measured[16].

Experimental design

To establish the optimal ischaemic preconditioning period as well as the time range of the subsequent warm ischaemia protected by such a manoeuvre, a preliminary study was performed. First, 5 min ($n = 6$) or 10 min ($n = 3$) of ischaemic preconditioning was compared with the control ($n = 6$) at 60 min after reperfusion following 60 min of warm ischemia. The interval between the preconditioning and subsequent long ischaemia was the same as for the period of ischaemic preconditioning (*Figs 1a* and *1b*). The animals were killed after sampling blood from the inferior vena cava. Mean(s.d.) alanine aminotransferase (AST) and lactic dehydrogenase (LDH) levels of the livers with 5 min of ischaemic preconditioning, 10 min of ischaemic preconditioning and without ischaemic preconditioning showed no significant differences (AST 3525(1418), 4801(1482) and 3677(1546) units/l; LDH 49 639(1760), 55 079(2436) and 39 605(3898) units/l respectively). Since ischaemia–reperfusion injury caused by 60 min of warm ischaemia seemed too severe, the ischaemic period was shortened to 40 min, while the ischaemic preconditioning time and reperfusion time were unchanged (5 min, 10 min and control; $n = 5$, 10 and 10 respectively). AST and LDH levels for each group were 983(193), 944(175) and 1349(593) units/l, and 8899(4273), 6259(1699) and 11 080(6828) units/l respectively. Animals with 10 min of ischaemic preconditioning had significantly lower AST and LDH values than those in the other groups. From these results, the periods of ischaemic preconditioning and subsequent warm ischaemia used in subsequent experiments were 10 min and 40 min, respectively. At the same time, reperfusion time was extended to 120 min[14]. The animals were divided into two groups: group 1 ($n = 10$) without ischaemic preconditioning (control) and group 2 ($n = 10$) with 10 min of ischaemic preconditioning.

The animals were killed after sampling blood from the inferior vena cava after 120 min of reperfusion. Liver samples were excised from the anterior edge of the median lobe before ischaemia, after the induction of ischaemia and 120 min after reperfusion. The specimens were immersed in liquid nitrogen immediately after sampling to measure the tissue concentration of adenine nucleotides, adenosine 5′-triphosphate (ATP), adenosine 5′-diphosphate (ADP), adenosine 5′-monophosphate (AMP) and total adenine nucleotides. At 120 min after reperfusion, the livers were perfused and fixed *in situ* with 4 per cent paraformaldehyde, 0·25 per cent glutaraldehyde and phosphate-buffered saline through the portal vein. To evaluate long-term effects of ischaemic preconditioning on the liver, five more animals in each group underwent the same procedure and were killed after 24 h of reperfusion.

Measurement of serum cytosolic enzymes

Serum ALT and LDH values were measured at 4°C using commercially available kits (Wako Pure Chemicals, Osaka, Japan).

Measurement of bile output

Bile output from the ischaemic liver was measured through a choledochotomy tube placed in the common bile duct.

Energy metabolism

ATP and its metabolites, ADP and AMP, in the liver tissue were assayed as follows. After grinding the frozen tissue with a mortar and pestle, the powder was mixed with 1 ml 6 per cent perchloric acid at 4°C. The mixture was centrifuged at 3000 r.p.m. for 10 min and the supernatant was stored at 4°C, then 0·5 ml 6 per cent perchloric acid was added to the precipitate and centrifuged in the same manner. The supernatant was neutralized with 3 mol/l potassium carbonate and centrifuged at 3000 r.p.m. for 10 min. The final supernatant was used as a sample for ATP and its metabolites. Pellets of liver tissue were used to determine the protein content, using a protein assay kit (Bio-Rad, Tokyo, Japan)[17]. The tissue concentration of ATP and its metabolites was determined by high-performance liquid chromatography (Shimadzu, Kyoto, Japan)[18] at a flow rate of 1·0 ml/min. The results were calculated as micromoles of nucleotide per gram of liver protein, and expressed as the percentage of values before ischaemia.

Histological examination

The excised liver was sliced into ten pieces, fixed in 20 per cent formalin and embedded in paraffin. Sections 3 μm thick were

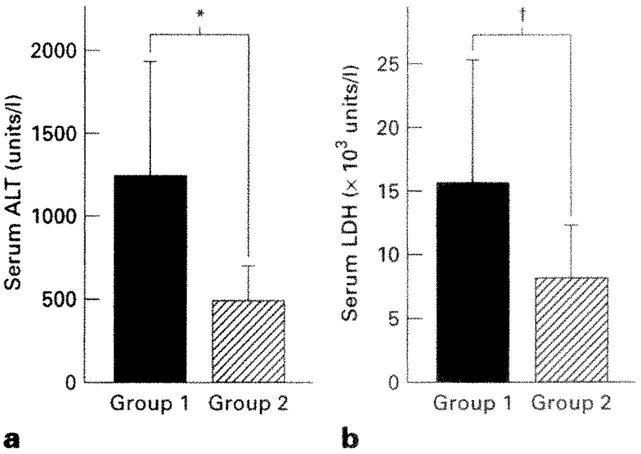

Fig. 2 Mean(s.d.) **a** serum alanine aminotransferase (AST) and **b** lactic dehydrogenase (LDH) levels after 40 min of warm ischaemia and 120 min of reperfusion in livers from animals subjected to no ischaemic preconditioning (group 1) or 10 min of ischaemic preconditioning (group 2). *$P < 0·005$, †$P < 0·05$ (Mann–Whitney U test)

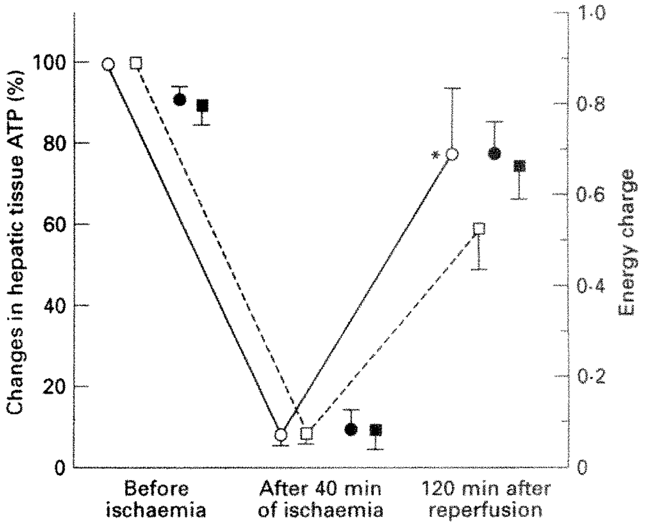

Fig. 3 Changes in adenosine 5′-triphosphate (ATP) levels (open symbols) and energy charge (closed symbols) in livers from animals subjected to no ischaemic preconditioning (group 1; □, ■) or 10 min of ischaemic preconditioning (group 2; ○, ●). Values are mean(s.d.). *$P < 0·05$ *versus* group 1 (Mann–Whitney U test)

stained with haematoxylin and eosin. For each liver studied, one section was chosen at random from the right medial, left medial and left lateral lobes. The size of necrotic and non-necrotic areas were measured from each liver slice with COSMOZONE 1S (Nikon, Tokyo, Japan). The necrosis rate was defined as the percentage necrotic area in the whole liver section, which was expressed as the mean of the percentage in three separate slices. The degree of liver damage was assessed by a liver pathologist (T.M.) who was blinded to the treatment given.

Statistical analysis

The Mann–Whitney *U* test was used for data analysis. $P < 0{\cdot}05$ was taken as significant.

Results

Fig. 2 demonstrates the serum ALT and LDH levels 120 min after reperfusion. Group 1 had significantly higher values than group 2 ($P < 0{\cdot}005$ and $P < 0{\cdot}05$ respectively). Serum ALT and LDH levels 24 h after reperfusion of the liver following 40 min of warm ischaemia with or without 10 min of ischaemic preconditioning were not significantly different between the two groups (ALT 296(71) *versus* 363(149) units/l; LDH 248(49) *versus* 252(97) units/l).

Group 2 livers produced more bile than those in group 1 during 120 min after reperfusion (0·12(0·03) *versus* 0·09(0·04) ml per g liver; $P < 0{\cdot}05$).

Fig. 3 exhibits the changes in ATP content and energy charge of the liver tissue. After reperfusion, group 2 demonstrated a rapid increase in ATP compared with group 1. On the other hand, there was no significant difference in the rate of reduction of ATP during ischaemia between the two groups. Changes in energy charge and levels of other metabolites such as AMP or ADP (data not shown) were not significantly different between the two groups during ischaemia or after reperfusion.

After 120 min of reperfusion the liver exhibited slight microvesicular steatosis of the hepatocytes in both groups, while hepatic necrosis was not present in either group (data not shown). At 24 h after reperfusion, group 1 livers demonstrated severe microvesicular steatosis of the hepatocytes, while in group 2 there was minimal microvesicular steatosis (*Fig. 4*). Furthermore, the extent of necrosis of the hepatic parenchyma was significantly

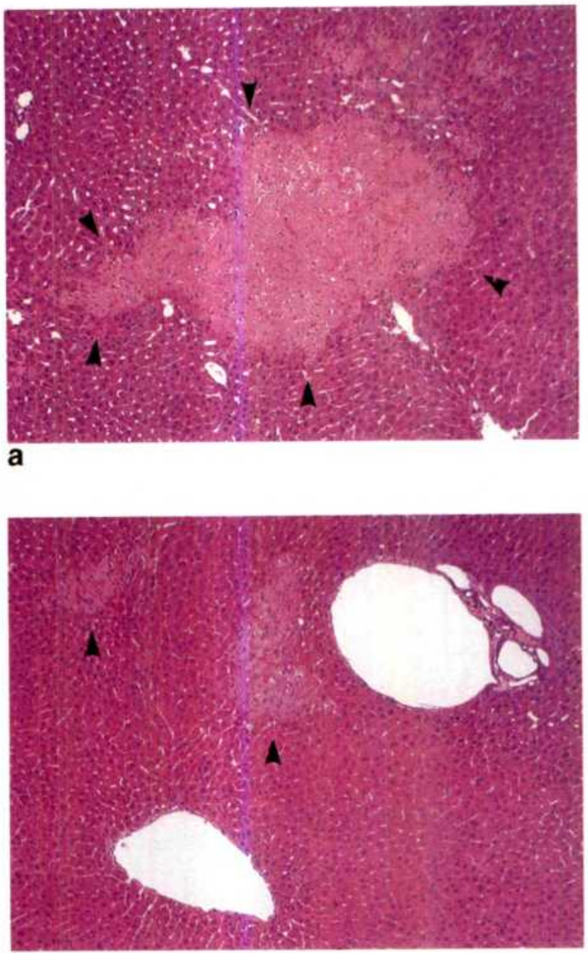

Fig. 4 Photomicrographs of the liver at 24 h after reperfusion following 40 min of warm ischaemia. **a** Group 1: there is scattered coagulative necrosis of the hepatic tissue (arrowheads). **b** Group 2: the necrosis is less prominent than that in the control (arrowheads). (Haematoxylin and eosin stain; original magnification ×40)

lower in group 2 (1·3(1·3) per cent) than group 1 (5·3(1·7) per cent) ($P < 0·05$).

Discussion

Since the first description by Pringle in 1908[19], temporary clamping of the hepatic pedicle has been used to obliterate the hepatic blood inflow in liver surgery. Although the liver can tolerate up to 60 min of warm ischaemia[20], intermittent ischaemia–reperfusion has been practised widely to avoid liver damage by prolonged warm ischaemia. A typical technique for such intermittent ischaemia–reperfusion consists of alternating hepatic pedicle occlusion for 15–30 min and 5–10 min of revascularization of the liver[21,22].

To date, attenuation of hepatic ischaemia–reperfusion injury has been achieved by exogenous administration of drugs and/or antibodies[23,24], which may be associated with systemic or hepatic side-effects. In this study, the presence of an endogenous defensive mechanism against ischaemia–reperfusion injury of the liver was demonstrated.

Using isolated perfusion of the liver, Dehni *et al.*[25] reported that 10 min of ischaemia–reperfusion protected the liver from a subsequent warm ischaemia of 90 min. In their study, the rat liver was perfused in a recirculating system with an oxygenated buffer. A single course of ischaemic preconditioning improved bile output and the perfusate concentrations of aspartate aminotransferase (AST) as well as LDH, while creatine kinase and vascular resistance were unchanged. Lloris-Carsi *et al.*[10] reported that a single ischaemic preconditioning of 5 min and reperfusion period of 10 min before 90 min of warm ischaemia improved 3-day survival, and that single or double brief ischaemic preconditioning and reperfusion decreased AST, ALT, LDH, malondialdehyde and myeloperoxidase levels on day 3 after perfusion. The effective preconditioning time based on preliminary experiments was 10 min. In the present study, however, 10 min of ischaemic preconditioning failed to demonstrate a significant difference in each parameter when followed by 60 min of warm ischaemia.

Murry *et al.*[26] proposed that the mechanism for protection of the myocardium in ischaemic preconditioning includes reduced myocardial energy demand which results in reduced utilization of high-energy phosphate and preservation of ATP. In the present experiment, although preservation of liver tissue ATP during ischaemia was not obvious, preconditioning did increase ATP immediately after reperfusion. The rapid recovery of ATP may signify the preservation of enzymes responsible for the production of ATP or the accumulation of ATP precursors during ischaemia. The recovery of tissue ATP is associated with rapid bile production after prolonged ischaemia of the liver[27]. Subsequent assessment showed differences in liver cell necrosis, at 24 h after reperfusion. This has been shown previously to be an adequate interval for assessment of changes in the extent of necrosis[15].

This study has demonstrated for the first time the advantage of ischaemic preconditioning on bile production, energy metabolism and hepatic necrosis *in vivo*. What seems to be a paradoxical phenomenon may be useful for the amelioration of hepatic ischaemia–reperfusion injury in hepatic resection and potentially in liver allografting.

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Survival following pancreatic carcinoma: a follow-up study of all cases recorded in Malmö, Sweden, 1977–1991

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Background The aim of this follow-up study was to assess whether there has been any increase in the percentage of patients offered attempted curative surgery for pancreatic carcinoma and whether the overall survival rate has improved, during the time period 1977–1991.

Methods Details of new cases of pancreatic carcinoma arising in the population of Malmö during the study period were retrieved from the Local Tumour Register in Lund, Sweden. In all, 740 patients were found; 575 of these were diagnosed before death. Kaplan–Meier analysis was used to calculate overall survival rates, and Cox regression analysis was used to assess survival in relation to year of diagnosis after adjustment for sex, age at diagnosis and stage of disease.

Results Cytological or histopathological evidence of the disease was given in 95 per cent of cases. The overall 5-year survival rate was 0·5 per cent (three of 575). Curative surgery was attempted in 24 patients (4·2 per cent); the proportion undergoing curative surgery increased in the last part of the study. Two of the 24 patients in this group survived for 5 years.

Conclusion The prognosis in pancreatic carcinoma remains dismal. Attempted curative surgery still is the only hope for cure, but the group of patients that can be offered this possibility is very limited. In this study, an increase was found in the proportion of patients who were offered attempted curative surgery, but there was no statistically significant increase in the 5-year survival rate following surgery.

The high survival rates, given by several follow-up studies of patients operated on for pancreatic carcinoma, may be interpreted as evidence of an improved prognosis[1–3]. Other studies have, however, presented results indicating that no or extremely few patients can be cured by surgery[4–7].

The objective of this study on pancreatic carcinoma from Malmö University Hospital, Sweden, was to assess whether there had been any increase in the percentage of patients offered attempted curative surgery and whether the overall survival rate improved during the time period 1977–1991.

Patients and methods

Few patients were offered attempted curative surgery before the end of the 1970s, and therefore the period 1977–1991 was chosen for study. This also permits an actual 5-year follow-up time. The study comprised all individuals belonging to the Malmö population who had carcinoma of the pancreas diagnosed during the period, as reported to the Local Tumour Register for Southern Sweden, in Lund. Reporting of cancer cases is compulsory, and is done by the surgeon or physician at the hospital, or by the local GP, as well as by the pathologist.

Of 740 reported carcinomas, 575 were diagnosed before death. Only pancreatic adenocarcinomas judged to be of ductal origin were included. The city of Malmö had a population that ranged between 229 107 and 240 220 during the study interval. The University Hospital is the only hospital in Malmö for admission of patients with somatic diseases, and so all patients with pancreatic carcinoma were seen by the surgeons there. All cytological and histopathological examinations, as well as autopsies, were performed at the Department of Pathology. During the 1970s and 1980s the clinical autopsy rate in the city was 65 per cent and in carcinoma cases it was 80 per cent or higher[8,9]. The material was entirely unselected. Three patients referred from outside Malmö were operated on in the early years of the study and were excluded. No other patients with pancreatic carcinoma were referred to this hospital from outside the city. No patients from Malmö were identified who were treated surgically outside the city. All cases have been followed from the time of diagnosis, as reported to the Local Tumour Register, until death or the end of 1996. No case was lost to follow-up.

To verify the diagnosis in all patients with pancreatic carcinoma surviving more than 2 years ($n = 19$), hospital charts including results from cytological and histopathological examinations and/or autopsy records were retrieved. All patients who had been operated on with attempted radical surgery ($n = 24$) were identified, and their charts were retrieved and scrutinized to verify that the operation was actually done with curative intent. This was true for all patients; these cases have already been reported in part[10].

Statistical analysis

The Kaplan–Meier method[11], with the generalized Wilcoxon rank sum test, was used for the computation of survival in relation to time at diagnosis, divided into three 5-year periods, and in relation to attempted curative surgery. Cox's proportional hazards model was used to estimate the probability of survival after attempted curative surgery during the two latest 5-year periods after adjustment for sex, age at diagnosis and stage of disease[12].

Results

During the 15-year study period, 740 patients with pancreatic adenocarcinoma were reported to the Local Tumour Register for Southern Sweden. One hundred and sixty-five patients (22·2 per cent) were diagnosed at autopsy. In 114 (69·1 per cent) of these, the underlying cause of death, according to death certificate, was pancreatic carcinoma.

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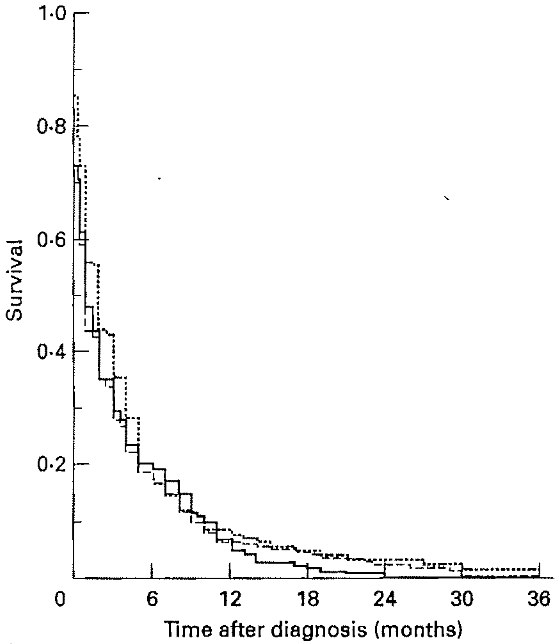
The median age of the 575 patients diagnosed while alive was 72 (range 38–96) years. In 411 (71·5 per cent) of these, the diagnosis was based on histopathology, in a further 138 (24·0 per cent) on cytology and in the remaining 26 (4·5 per cent) the diagnosis was made by ultrasonography, computed tomography (CT) or surgical exploration without a cytological or histopathological examination.

For the whole cohort of 740 patients, there was no difference in survival between the 5-year periods (*Fig. 1*) (cases identified at autopsy were included and given a fictive survival of 0·1 month). Patients selected for attempted radical surgery were younger at diagnosis and survived longer than those treated by palliative surgery or no surgery at all (*Table 1*). The resection rate during the first 8 years of study was 1·9 per cent (five of 261) and in the last 7 years it was 6·1 per cent (19 of 314) ($P < 0{\cdot}05$). The 19 patients who survived more than 2 years all had cytological or histopathological confirmation of adenocarcinoma of the pancreas. Eight of these were operated on with curative intent; the rest were generally treated with bypass surgery.



No. at risk

	0	6	12	18	24	30	36
1977–1981	220	42	12	5	1	1	0
1982–1986	262	44	18	12	7	2	1
1987–1991	255	42	21	13	9	6	5

Fig. 1 Kaplan–Meier survival curves, illustrating survival for 740 new patients with pancreatic carcinoma diagnosed in 1977–1981 (————), 1982–1986 (– – – –) and 1987–1991 (······). The number of patients remaining alive and in the study at the beginning of each 6-month period is shown below the graph

Table 1 Age and survival related to mode of treatment

	Age (years)	Survival (months)
Attempted radical surgery (*n* = 24)	60 (42–74)	11 (2–109)
Palliative or no surgery (*n* = 551)	72 (38–96)	2 (0–71)
Cases identified at autopsy (*n* = 165)	80 (60–101)	—
All cases (*n* = 740)	74 (38–101)	1 (0–109)

Values are median (range)

Palliative operations (biliary or gastric bypasses) were undertaken in 281 patients (48·9 per cent). In 95 per cent of the operated cases this meant a biliodigestive shunt and/or a gastrojejunostomy. Laparotomy without additional procedures was performed in five patients (0·9 per cent). Endoscopic stenting, in patients jaundiced as a result of pancreatic tumour obstructing the common bile duct, was not in regular use at this time. During the 3 years preceding 1991, an endoscopic stent was used in five patients.

Twenty-four patients (4·2 per cent) were selected for attempted curative surgery and underwent a Whipple procedure (*n* = 21); in one case a total and in two a distal pancreatectomy was performed. The presenting symptoms for these patients are shown in *Table 2*. Only one patient was operated on in the first time period, eight in the second and 15 patients in the third. All had findings of ductal adenocarcinoma (*Table 3*), in 22 cases in the head and in two in the tail of the pancreas[13]. All survived for 30 days. One patient died after 52 days and several reoperations. Twenty-two of the 24 patients died within 5 years, all from recurrent disease; in 16 patients there was locoregional recurrence and 15 had distant

Table 2 Presenting symptoms in patients undergoing pancreatic resection. Symptoms were present for a median of 1 (range 0·5–9) months

Symptom	No. of patients
Jaundice	18
Pain	12
Nausea and vomiting	3
Diarrhoea	2
Weight loss	8

Eighteen patients were admitted on an emergency basis

Table 3 Tumour grade, tumour node metastasis classification and stage in patients who had a pancreatic resection

	No. of patients
Tumour grade	
High	9
Intermediate*	9
Low	6
TNM classification†	
T_1N_0	4
T_1N_1	3
T_2N_0	11
T_2N_1	4
T_3N_0	1
T_3N_1	1
T_4 any N	0
Stage‡	
I	15
II	1
III	8

*Intermediate differentiation; †Union Internacional Contra la Cancrum tumour node metastasis (TNM) classification, 1987; ‡stage I, $T_1T_2N_0M_0$; stage II, $T_3N_0M_0$; stage III, any TN_1M_0. One patient (stage I/T_2N_0) died in hospital 52 days after operation. The two 5-year survivors had stage I(T_2N_0) and stage III(T_1N_1) disease metastases. The diagnosis of recurrent disease was based on autopsy in 13 cases, and in the remaining nine on CT or ultrasonography, often together with fine-needle aspiration biopsy. Median survival time was 11 months. Two patients, at the time of writing aged 59 and 81 years, are still alive and free from disease 8 and 9 years after resection; one of these patients had a distal carcinoma.

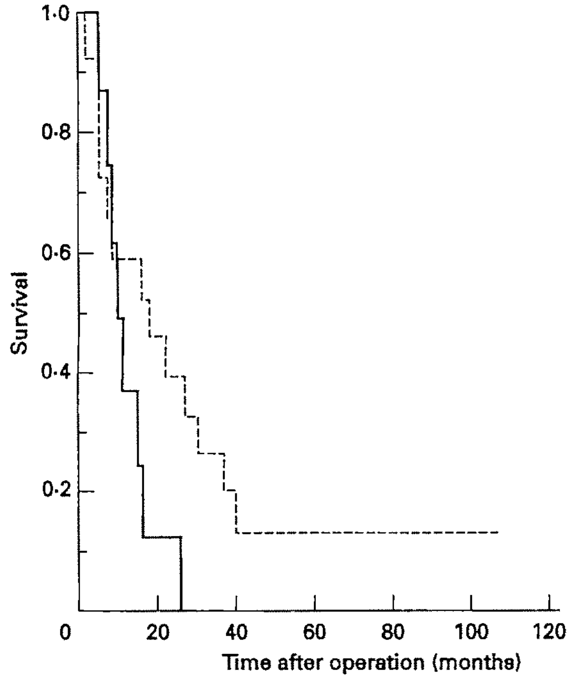
The 5-year survival rate for patients operated on between 1987 and 1991 was not statistically significantly different from that of those undergoing operation between 1982 and 1986 (*Fig. 2*) (relative risk 0·5 (95 per cent confidence interval 0·2–1·4); $P = 0{\cdot}2$).

For all patients diagnosed while alive, the 5-year survival rate was 0·5 per cent (three of 575); for the entire cohort, i.e. including the cases detected at autopsy, it was 0·4 per cent (three of 740).

Among those not operated on, or not operated on for cure, three patients (0·5 per cent) lived longer than 3 years and one is still alive 6 years later. This patient had an adenocarcinoma *in situ* in a surgical biopsy. Resection was not done owing to a severe inflammatory reaction in the surrounding tissues. The specimen has been re-evaluated and the diagnosis confirmed.

Discussion

Pancreatic carcinoma was in this study associated with an overall 5-year survival rate close to zero. From this perspective the survival rate of 8 per cent (two of 24) in patients who were offered attempted curative surgery may be considered a great therapeutic achievement.



No. at risk

1982–1986	8	1	0	0	0	0
1987–1991	14	6	2	2	2	2

Fig. 2 Kaplan–Meier survival curves, illustrating survival following attempted radical surgery for pancreatic carcinoma for the periods 1982–1986 (————) and 1987–1991 (– – – –). The number of patients remaining alive and in the study at the beginning of each 20-month period is shown below the graph

These figures are, however, far from the 25–55 per cent survival rates reported in other follow-up studies[7]. It is likely that these discrepancies do not reflect differences in therapeutic success, but rather the selection of cases used for assessment of survival rates. In this study all cases of pancreatic carcinoma during the time period 1977–1991 were included. As the university hospital is the only referral unit for somatic disorders and as the autopsy rate during the study period was almost 70 per cent, the authors are confident that the patients included can be considered a representative sample of the population with pancreatic carcinoma in Malmö.

The low number of survivors in this study was not the result of inadequate surgical technique or perioperative care. The 30-day mortality rate was zero and one patient died in hospital following resection; these figures are comparable to results from units doing pancreatic surgery on a regular basis[14–16].

The resection rate in this study was 4·2 per cent, whereas the usual reported figure is around 10 per cent or more[7,15,17]. The main reason for the difference is probably that material in the present study was entirely unselected. The local or national attitude to resectional surgery may also be more conservative, and may be reflected in lower resection rates.

The lack of significant differences in 5-year survival rates for patients operated on in the periods 1982–1986 and 1987–1991 must be considered in relation to the small numbers of patients.

The high rate of local recurrence is well documented, and is probably due to local spread of the tumour before diagnosis[18,19]. Adjuvant treatment directed towards the peripancreatic region could possibly improve survival[20–22]. The large multicentre trial, being conducted by the European Study Group of Pancreatic Cancer, may clarify the role of adjuvant treatment[23]. However, an adjuvant treatment will have to be extremely effective for that alone to result in an improvement on the dismal survival figures of today. A reduced death rate of 30 per cent with adjuvant treatment has been indicated for colonic cancer[24]. A corresponding effect in pancreatic carcinoma would, with the present resection rate, result in a change of survival rate from 8 per cent to about 30 per cent in patients operated on with curative intent. In actual numbers this is equal to six more 5-year survivors, an increase from two to eight.

Is the present resectability rate low, or is it representative of the true rate in an unselected population of carcinoma cases? A large epidemiological study on the outcome of nearly 14 000 unselected cases of pancreatic carcinoma in the West Midlands, UK, recently reported a resection rate of 2·6 per cent[25]. There are considerable differences between the two studies. The age-standardized incidence of the disease was 10·1 and 8·4 per 10^5 for men and women respectively in the Midlands[25]. In Malmö the incidence was 20·6 and 13·4 per 10^5 respectively during the 1980s[26]. The number of patients included in the Swedish study was substantially lower than in the UK study, but the diagnosis was to a high degree verified by cytological (24·0 per cent) or histological (71·5 per cent) examination. Despite these differences, both studies arrived at the same rate of palliative procedures, as well as similar resection and survival rates. As in this study, the British group also found an increased 5-year survival rate after resection in the most recent period.

Resection rates in unselected patients with pancreatic carcinoma do not seem to be higher than 5–10 per cent, and the 5-year survival rate after attempted curative surgery is less than 10 per cent. The resection rate during the last 7 years of the present study was not far from the 7 per cent reported from a Norwegian national study[27]. This means that, up to 1991, one in 200 patients with pancreatic carcinoma was 'cured' by surgery, at best. Low resection rates may be due to a nihilistic view of the possibilities of surgery, but the authors believe that resection rates over 10 per cent are probably the result of patient selection.

In this urban population, the proportion of patients with pancreatic carcinoma who may be offered attempted curative surgery has increased from 1·9 per cent in 1977–1984 to 6·1 per cent in 1985–1991. The seemingly improved 5-year survival rate was not statistically significant in the Cox analysis after adjusting for sex, age at operation and stage of disease. It must be emphasized, however, that this part of the study was based on a very limited number of patients.

Acknowledgements

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Splenic complications in chronic pancreatitis: prevalence and risk factors in a medical–surgical series of 500 patients

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Background The prevalence, course, treatment, outcome and risk factors of splenic complications in chronic pancreatitis are poorly documented.

Methods Patients with splenic complications in a medical–surgical series of 500 consecutive patients with proven chronic pancreatitis prospectively followed up for a mean of 7·0 years were compared with patients without splenic complications.

Results Eleven men (2·2 per cent) with alcoholic chronic pancreatitis (median duration 2 (range 0–5) years) had a splenic complication: intrasplenic pseudocyst ($n = 5$), subcapsular haematoma ($n = 2$) or splenic rupture ($n = 4$). All patients except one underwent splenectomy, five of whom also underwent distal pancreatectomy. There were no deaths. Patients with splenic complications had pancreatic tail necrosis (six of 11 *versus* 17·4 per cent; $P = 0{\cdot}007$), distal pseudocyst (six of 11 *versus* 11·7 per cent; $P = 0{\cdot}0009$) or splenic vein occlusion (seven of 11 *versus* 10·8 per cent; $P < 0{\cdot}0001$) more frequently than those without. In the 22 patients with distal pseudocyst and splenic vein occlusion, the prevalence of splenic complications was 18 per cent (odds ratio 15·0 (95 per cent confidence interval 4·0–55·7).

Conclusion Splenic complications occur early in the course of chronic pancreatitis, are rare and are favoured by splenic vein occlusion and pseudocyst or necrosis of the pancreatic tail. Surgical treatment is usually required.

Despite its close proximity to the pancreas, the spleen is rarely involved in the complications of chronic pancreatitis[1–4]. In large surgical series, fewer than 5 per cent of patients with chronic pancreatitis underwent surgery for splenic complications[1,2,5,6]. Splenic vascular complications[5–7], intrasplenic pancreatic pseudocyst, abscess, subcapsular haematoma, infarction, necrosis and splenic rupture have all been reported[1–3], but the overall incidence and clinical features are not clear[1]. Recognition of splenic complications is important because splenectomy is often indicated. This study examined the incidence, clinical features and risk factors of splenic complications in a large medical–surgical series of patients with chronic pancreatitis.

Patients and methods

Five hundred consecutive patients with chronic pancreatitis attending the authors' medical and surgical gastroenterological units between 1973 and 1996 were studied. Patients were seen as outpatients once a year, or when required for symptoms or complications thought to be related to chronic pancreatitis. At each attendance, patients underwent clinical assessment, routine laboratory tests, and either abdominal computed tomography (CT) (since 1978) or ultrasonography. Data were then registered prospectively in a database.

The diagnosis of chronic pancreatitis was established on one or more of the three criteria: (1) pancreatic calcifications as seen on abdominal plain films or CT; (2) moderate to marked ductal lesions ('Cambridge' criteria)[8]; and (3) typical histology of an adequate surgical specimen. Marked exocrine insufficiency (steatorrhoea more than 7 g fat per 24 h) of proven pancreatic origin was also accepted as evidence of chronic pancreatitis[9]. Alcoholic chronic pancreatitis was diagnosed when alcohol intake exceeded 60 g/day for at least 2 years in the absence of other causes; chronic pancreatitis was considered 'idiopathic' when no cause was found[9].

Splenic vein occlusion was systematically searched for using ultrasonography in all patients and then confirmed by angiography, contrast-enhanced CT or surgery[7]. Isolated splenic vein occlusion and splenic artery pseudoaneurysms were not considered as splenic complications in this study[1,5,7].

Attacks of necrotizing acute pancreatitis superimposed on chronic pancreatitis (acute exacerbations of chronic pancreatitis) were diagnosed on clinical and biochemical criteria (acute abdominal pain requiring hospitalization and associated with raised pancreatic enzyme levels above three times the upper limit of normal values) and radiological, intraoperative or pathological findings consistent with the presence of pancreatic or extrapancreatic necrosis, abscess or fat necrosis[10]. Altogether, 273 patients (54·6 per cent) had at least one attack of acute pancreatitis. Other causes of acute pancreatitis, unrelated to chronic pancreatitis, such as gallstones, hypercalcaemia, or hypertriglyceridaemia, were systematically ruled out[10].

Pancreatic pseudocysts were diagnosed on radiological, intraoperative or pathological data[9]. In this study, 'distal pseudocysts' were pseudocysts involving the pancreatic tail or located in the splenic hilum.

Splenic complications were suspected on clinical and radiological grounds, and confirmed by surgery and pathological examination of the resected specimen in all but one patient.

Clinical and radiological data from patients with and without splenic complications were retrieved and compared. Results are expressed as mean(s.d.), median (range) or percentages, as appropriate. Adjusted odds ratios with two-sided 95 per cent confidence intervals are provided. Categorical variables were compared by the χ^2 test; Yates' correction or Fisher's exact test was used when appropriate. Continuous variables were compared by the Student's t test or Mann–Whitney U test when

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appropriate. The level of statistical significance was set at $P = 0.05$.

Results

Alcohol was the cause of chronic pancreatitis in 423 patients (84·6 per cent). Besides 'idiopathic' chronic pancreatitis ($n = 60$; 12·0 per cent), the causes of non-alcoholic chronic pancreatitis[9] were hereditary chronic pancreatitis ($n = 8$), abdominal radiotherapy ($n = 4$), inflammatory bowel disease ($n = 3$) and Sjögren's syndrome ($n = 2$). The mean(s.d.) follow-up was 7·0(6·7) (range 0–35) years, for a total of 4086 patient-years. Among the 500 patients, 237 underwent pancreatic resections or drainage procedures. The 148 patients (29·6 per cent) lost to follow-up did not differ from the 352 other patients, except for a longer follow-up (8·4(7·0) *versus* 6·9(6·6) years; $P = 0.02$). Splenic complications occurred in 11 patients. The general characteristics of patients with chronic pancreatitis with and without splenic complications are recorded in *Table 1*.

Among the 500 patients, 11 men (2·2 per cent) of median age 39 (range 27–51) years, in whom alcohol was the cause of chronic pancreatitis, developed a splenic complication: five had an intrasplenic pseudocyst (*Figs 1* and *2*), two had an intrasplenic subcapsular haematoma and four had a splenic rupture (*Fig. 3*). This represented one case for every 371 patient-years of follow-up. The median duration of symptoms of chronic pancreatitis at

Table 1 General characteristics of patients with chronic pancreatitis with and without splenic complications

	With splenic complications ($n = 11$)	Without splenic complications ($n = 489$)
Men	11(100)	415(84·9)
Alcoholic aetiology of chronic pancreatitis (%)	11(100)	412(84·2)
Pancreatic calcifications (%)	7(64)	356(72·8)
Age at onset of chronic pancreatitis (years)*	36·9(6·1)	41·4(13·0)
Age at diagnosis of chronic pancreatitis (years)*	39·0(6·2)	43·4(13·3)
Follow-up (years)*	6·6(3·1)	7·0(6·7)

*Values are mean(s.d.). There were no significant differences for comparisons between patients with and without splenic complications

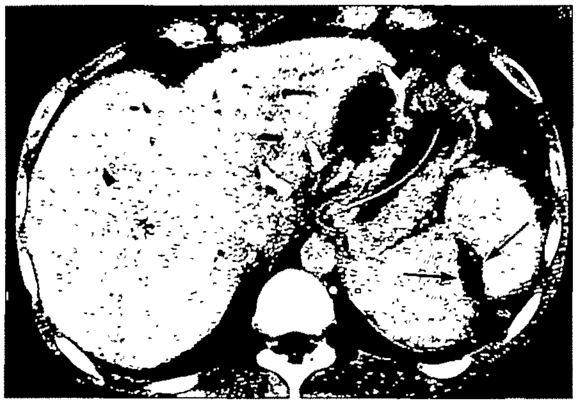

Fig. 1 Computed tomography scan after contrast injection showing intrasplenic pseudocyst (arrows) and splenic vein occlusion causing segmental portal hypertension with enlargement of the gastroepiploic vein (arrowheads)

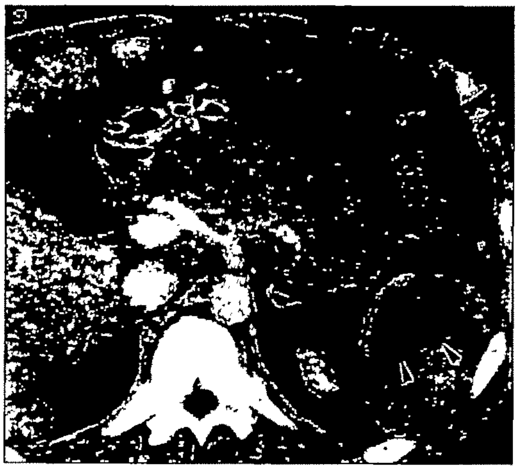

Fig. 2 Computed tomography scan after contrast injection showing intrasplenic pseudocyst (arrowheads) in a patient with recent acute pancreatitis

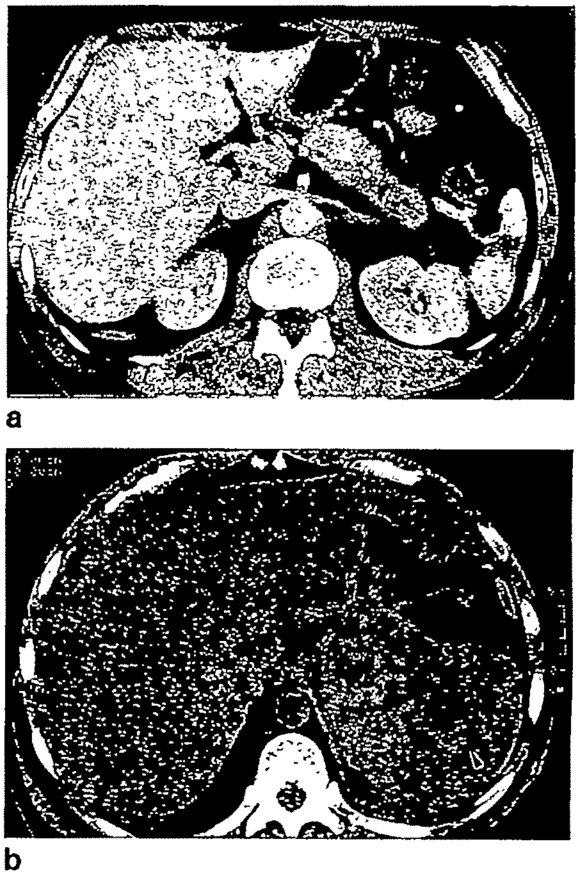

Fig. 3 **a** Computed tomography scan after contrast injection showing main pancreatic duct lithiasis and splenic vein occlusion causing segmental portal hypertension. **b** Scan 1 year later showing a splenic rupture; there is spontaneous hyperdensity of the spleen before contrast injection due to a large haematoma (arrowheads) which developed after minimal abdominal trauma the time of diagnosis of the splenic complication was 2 (range 0–5) years. Chronic pancreatitis presented with splenic complications in two patients. Exocrine or endocrine pancreatic insufficiency was observed in none and one patient at the time of diagnosis of a splenic complication respectively.

The clinical features of patients with splenic complications are shown in *Table 2*. Three clinical signs were seen alone or in combination in all patients but one: left-upper quadrant abdominal pain ($n = 10$) referred to the left shoulder ($n = 6$), left-sided pancreatic pleural effusion (in three of five patients with intrasplenic pseudocysts) and circulatory collapse (in three of four patients with splenic rupture). A right-sided pleural effusion, haemorrhagic and with high amylase content, was observed in one patient with splenic rupture. Fever was present in six patients. Splenic rupture occurred following minimal abdominal trauma (fall on a boat deck) in one patient, but spontaneously in the other three. Normocytic anaemia (haemoglobin level 5·1–8·8 g/dl) was observed in all patients with splenic rupture, but in none of those with subcapsular haematoma. Inflammatory microcytic anaemia (haemoglobin level 9·6–11·8 g/dl) was noted in four of five patients with intrasplenic pseudocysts. Biochemical evidence of inflammation was noted in nine patients. Leucocytosis was noted in six patients and was above 20 000 per mm^3 in five of them, including three patients with splenic rupture. Pancreatic enzyme levels were more than three times above the upper limit of normal values in seven patients. Distal pseudocysts ($n = 6$) and/or acute exacerbation of chronic pancreatitis with necrosis of the pancreatic tail ($n = 6$) were seen in all patients except one with a history of trauma (*Fig. 3*). Marked distal lesions of the main pancreatic duct ($n = 5$) were found in four of six patients with distal pseudocysts. Taken altogether, abdominal ultrasonography, CT and arteriography (performed in two patients) suggested splenic complications in nine of 11 patients, demonstrated the type of splenic complication in seven patients and disclosed splenic vein occlusion in five patients (*Figs 1, 2* and *3*).

Table 2 Clinical characteristics and surgical procedures in 11 patients with chronic pancreatitis and splenic complications

	Pseudocyst ($n = 5$)	Rupture ($n = 4$)	Haematoma ($n = 2$)
Median (range) age (years)	39 (36–45)	36 (27–51)	47, 34
Median (range) duration of chronic pancreatitis (months)	7 (0–60)	60 (5–60)	11, 36
Distal pancreatic lesions			
Necrotizing acute pancreatitis	3	2	1
Pseudocyst	4	1	1
Marked ductal lesions	2	2	1
Surgical procedures			
Splenectomy	1	4*	1
Splenectomy and distal pancreatectomy	3	0	1

*Cystogastrostomy was also performed in one patient

One patient for whom surgery was initially planned did not undergo operation because the intrasplenic pseudocyst regressed spontaneously. Surgical procedures performed in the ten other patients are summarized in *Table 2*. Splenectomy was performed as an emergency in three of four patients with splenic rupture and in one patient with splenic haematoma. Distal pancreatectomy was performed in addition to splenectomy in three of four patients with marked ductal lesions, or when an inflammatory mass at the splenic hilum made dissection hazardous. Surgical examination showed haemoperitoneum with haematoma of the left hypochondrium in the four patients with splenic rupture. Inflammatory and often haemorrhagic perisplenic adhesions were noted in six patients, including the four with surgically treated intrasplenic pseudocysts but only one of four patients with splenic rupture. Splenic vein occlusion was found in seven patients including all four with splenic rupture. Two of these seven patients also had splenomegaly.

None of the patients died. Four of the six patients who underwent splenectomy, but only one of four patients who also underwent distal pancreatectomy, developed postoperative complications, notably pancreatic fistula ($n = 4$) and pancreatic pseudocysts or abscess ($n = 3$). Such complications led to distal pancreatectomy in one patient 15 days after splenectomy for rupture. Insulin-dependent diabetes mellitus developed after distal pancreatectomy in two patients.

In three of four patients with surgically treated intrasplenic pseudocysts, pathological examination of the resected specimen confirmed that intrasplenic pseudocysts developed by direct extension of distal pseudocysts. Fat necrosis was identified histologically in all patients treated surgically.

All patients with chronic pancreatitis with splenic complications had at least one of the following three lesions of the perisplenic area: pseudocysts, necrotizing acute pancreatitis or splenic vein occlusion. Their presence in chronic pancreatitis increased the risk of splenic complications (*Table 3*). No splenic complications occurred in the 341 patients with chronic pancreatitis

Table 3 Risk factors for splenic complications in patients with chronic pancreatitis

		Patients with chronic pancreatitis*			
Risk factor	Splenic complications (%)†	Without splenic complications ($n = 489$)	With splenic complications ($n = 11$)	Odds ratio‡	P
Necrotizing acute pancreatitis	7	85(17·4)	6(55)	5·7(1·7–19·1)	0·007
Distal pseudocyst	9	57(11·7)	6(55)	9·1(2·7–30·8)	0·0009
Splenic vein occlusion	12	53(10·8)	7(64)	14·4(4·1–50·8)	<0·0001
Splenic vein occlusion and distal pseudocyst	18	18(3·7)	4(36)	15·0(4·0–55·7)	0·0008
Splenic vein occlusion and necrotizing acute pancreatitis or distal pseudocyst	16	31(6·3)	6(55)	17·7(5·1–61·3)	<0·0001

Values in parentheses are *percentages or ‡95 per cent confidence intervals. †Percentage of patients with risk factor(s) who developed splenic complications

(68·2 per cent) without any of these risk factors ($P < 0·0001$).

Discussion

There were only 11 patients with splenic complications (2·2 per cent) among 500 with chronic pancreatitis for 4086 patient-years, representing one case for every 371 years of follow-up. Examination by abdominal ultrasonography or CT was performed at least yearly for all patients with chronic pancreatitis so it is unlikely that the incidence was underestimated. Intrasplenic pseudocyst was the most frequent complication in this series, followed by splenic rupture, which is in accordance with previous studies[1].

Pain referred to the left shoulder, left-sided pancreatic pleural effusion and circulatory collapse were seen alone or in combination in all patients but one in this series, and should warn the physician of the possibility of a splenic complication in a patient with chronic pancreatitis[1]. Although CT is reported to be highly accurate in the diagnosis of splenic complications[11], abdominal imaging did not establish the type of complication in four patients in this series.

Pseudocysts or necrotizing acute pancreatitis involving the pancreatic tail appear to be a prerequisite for splenic complications, as they were present in all patients except one who had a history of recent minimal abdominal trauma. It was found that splenic vein occlusion, which has been shown previously to be related to adjacent pseudocysts or acute necrotizing pancreatitis in 91·4 per cent of cases in chronic pancreatitis[7], dramatically increased the risk of splenic complications. This may explain why splenic complications always occurred within 5 years from the onset of chronic pancreatitis, when acute exacerbations of chronic pancreatitis and pseudocysts are also more common[9,12,13]. Splenic complications may even represent the first manifestation of chronic pancreatitis, as in two patients in this series[14].

Perisplenic adhesions ('perisplenitis') as a result of recurrent acute pancreatitis are thought to favour the onset of splenic rupture in patients with chronic pancreatitis[1,3] but were seen in only one of four patients in this series. By contrast, splenic vein occlusion was found in seven patients, and in all patients with splenic rupture. It perhaps contributed to the splenic rupture after minimal abdominal trauma in one patient. Venous hypertension may impair haemostasis and may form the basis of an argument against conservative therapeutic procedures for haemorrhagic splenic complications in patients with chronic pancreatitis[15].

Intrasplenic pancreatic pseudocysts most often develop by direct expansion of distal pseudocysts[1,3,4,16–18]. This occurred in four of five patients in the present series, representing 6 per cent of 63 patients with chronic pancreatitis with distal pseudocysts (*Table 3*). Liquefaction of splenic infarcts, pancreatitis occurring in ectopic intrasplenic pancreatic tissue, or proteolytic effects of pancreatic enzymes on splenic vessels or parenchyma may represent alternative mechanisms of development of intrasplenic pseudocysts[1–4]. Marked pancreatic ductal lesions may favour distal pseudocysts (as in four of six patients with distal pseudocysts in this series) and fistulous or inflammatory connections between the pancreas and the spleen, which may ultimately cause splenic complications in patients with chronic pancreatitis[3,16–18].

In this series, all patients except one were operated on, often as emergencies or because of the absence of spontaneous regression or even expansion of intrasplenic collections. Distal pancreatectomy performed in addition to splenectomy seemed to result in fewer pancreatic fistulas, perhaps by treating simultaneously splenic complications and associated lesions of the pancreatic tail. However, distal pancreatectomy may predispose to diabetes mellitus, as in two patients in this series. Percutaneous drainage of intrasplenic fluid collections, which could facilitate or even prevent the need for surgery but which may also result in intraperitoneal haemorrhage, was not used in this series[19–22]. Expectant management of intrasplenic fluid collections may be hazardous, first, because the spontaneous regression of splenic subcapsular haematomas occurring within the course of chronic pancreatitis is unlikely in the presence of segmental portal hypertension[15] and, second, because the risk of rupture or infection of intrasplenic pseudocysts is high[1–4,23,24].

In conclusion, splenic complications occurred in 2·2 per cent of a medical–surgical series of 500 consecutive patients with chronic pancreatitis, with an incidence of one episode per 371 patient-years. Clinical features were abdominal pain radiating to the left shoulder, left-sided pleural effusion and haemodynamic instability. Risk factors were distal pseudocysts, acute exacerbations with necrosis of the pancreatic tail and splenic vein occlusion. Surgical treatment was usually required. Patients undergoing concomitant distal pancreatectomy had a lower rate of postoperative fistula.

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Long-term outcome of necrotizing pancreatitis treated by necrosectomy

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Background Long-term functional outcome after operative treatment of necrotizing pancreatitis (NP) has not been studied extensively.

Methods Pancreatic function, performance status, recurrence of symptoms and other related problems were analysed in 44 consecutive patients successfully discharged from hospital after operative necrosectomy (1983–1995) and followed up completely for a mean of 5 years.

Results Clinical pancreatic insufficiency developed in half the patients. Diabetes mellitus (11 patients), steatorrhoea (six) or both (five) were associated with a mean estimate of 52, 66 and 67 per cent parenchymal necrosis respectively. Normal pancreatic function was associated with 27 per cent parenchymal necrosis ($P < 0{\cdot}05$). Diabetes worsened while steatorrhoea tended to improve over time. Abdominal pain and pancreatitis recurred in six and two patients respectively. Performance status worsened in four patients because of recurrent pancreatitis and severe steatorrhoea. Poor long-term performance was associated with a higher Acute Physiology And Chronic Health Evaluation II score on admission (mean 14 *versus* 9).

Conclusion NP has prominent effects on long-term pancreatic exocrine and endocrine function in half the patients, but most preserve a good overall functional status. The development of pancreatic insufficiency varies with the extent of pancreatic parenchymal necrosis.

Although necrotizing pancreatitis (NP) accounts for only 3–5 per cent of all cases of acute pancreatitis (AP), it is responsible for most of the deaths related to this disease. Despite recent advances in the understanding of the pathophysiology of NP leading to improved management, mortality rates remain high (14–28 per cent)[1–3] and significant perioperative morbidity often exceeds 50 per cent[1–4]. Thus, clinical research in NP has been aimed at decreasing early morbidity and mortality rates (immediate outcome). However, detailed information is lacking on the long-term outcome of NP in terms of pancreatic exocrine and endocrine function, recurrent pancreatitis, performance status and other related complications after successful operative treatment. The hospital course of patients after operative treatment of NP has been described previously[4] and the long-term follow-up is now reported.

Patients and methods

Data were collected prospectively on 72 consecutive patients with NP treated at this institution between 1983 and 1995 by operative necrosectomy, as described previously[2,4]. Diagnosis of NP was made with contrast-enhanced computed tomography (CT) and confirmed at operation[5]. Indications for operation included positive cultures from percutaneous aspirates ($n = 32$), extraluminal gas on CT ($n = 21$) or clinical deterioration ($n = 19$)[4]. Only patients with pancreatic or peripancreatic necrosis confirmed at operation were included. The Atlanta classification of NP[6] was used. Because most patients were transferred to this institution after the onset of AP, severity was determined by the Acute Physiology And Chronic Health Evaluation (APACHE) II score at that time. Extent of pancreatic parenchymal necrosis was estimated as a percentage based on a combination of contrast-enhanced CT and intraoperative findings.

The hospital mortality rate was 25 per cent[4]. Follow-up of the 54 patients discharged from the hospital was based on clinic visits and on a standardized questionnaire obtained during the last contact, either in person or by telephone. Patients were evaluated for development of clinically evident endocrine pancreatic insufficiency, exocrine pancreatic insufficiency, recurrent pancreatitis, abdominal pain, incisional hernia, performance status and ability to return to work. Endocrine pancreatic insufficiency was defined as development of diabetes mellitus (fasting glucose higher than 200 mg/dl in repeated measurements) in patients who were euglycaemic before NP, or had non-insulin-dependent diabetes mellitus before NP and became insulin dependent subsequently. Patients who developed significant changes in bowel habit (frequency and/or consistency) underwent studies of faecal fat excretion; when increased to greater than 7 g per 24 h or 20 per cent in weight, exocrine pancreatic insufficiency was diagnosed. Diagnosis of recurrent pancreatitis was made when the typical clinical pattern of abdominal pain was associated with hyperamylasaemia. Determination of performance status was based on the Eastern Cooperative Oncology Group (ECOG) score[7], as is routine in this institution for chronically ill patients.

Development of pancreatic insufficiency was correlated with the extent of estimated pancreatic parenchymal necrosis and expressed as mean(s.e.m.) percentage necrosis. Necrosis of the head and neck of the gland was considered as 50 per cent, of the body 30 per cent and of the tail 20 per cent. Attempts were made to correlate development of recurrent pancreatitis, abdominal pain, deterioration of performance status and inability to return to work with the APACHE II score on admission to this institution, extent of parenchymal necrosis, presence of pancreaticocutaneous and gastrointestinal fistulas, and intensive care unit (ICU) and total hospital stay. Statistical comparisons were made using analysis of variance (ANOVA) and two-sample t tests for continuous variables, and Fisher's exact test when proportions were compared.

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Results

Between 1983 and 1995, 54 patients were discharged from this institution after operative treatment of NP. Ten died during follow-up. Two died from complications of NP within 1 month of discharge; eight others died from unrelated causes between 1 and 4 years later. Causes included cardiovascular events (four patients), perforated appendicitis, perforated duodenal ulcer, colon cancer and unknown (one each).

The remaining 44 patients comprise the study group. There were 33 men and 11 women, with a mean age of 58 (range 20–93) years. The aetiology of NP was gallstones in 17, idiopathic in 12, postoperative and alcohol-related in five each, endoscopic retrograde cholangiopancreatography (ERCP)-induced in four (none of whom had chronic pancreatitis) and hereditary in one. All patients were followed to the present with a mean follow-up of 60 (median 48 (range 3–132)) months.

Pancreatic function

Twenty-two patients maintained normal endocrine and exocrine pancreatic function, whereas 11 developed endocrine insufficiency alone, six exocrine insufficiency alone, and five both endocrine and exocrine insufficiency. There was no apparent association between the aetiology of NP and the development of pancreatic insufficiency. After alcohol-related NP, three patients maintained normal pancreatic function and one each developed endocrine or exocrine pancreatic insufficiency.

Endocrine pancreatic insufficiency. A total of 16 patients developed endocrine insufficiency, either alone (11) or in combination with exocrine insufficiency (five). Four required insulin perioperatively but were discharged on, and have been managed since with, diet and oral hypoglycaemic agents. The remaining 12 patients developed insulin-dependent diabetes mellitus, one of whom had been treated with oral hypoglycaemic agents for glucose control before the onset of NP. Eleven patients developed diabetes before hospital discharge and the remaining five after a median of 2 (range 1–8) years. These five patients did not have associated exocrine insufficiency and they comprised almost half of those with endocrine insufficiency alone. Once established, endocrine insufficiency tended to deteriorate with time or, at best, remain stable. Ten patients required increasing doses of insulin during follow-up; three were diagnosed as having 'brittle' diabetes and one developed secondary complications of diabetes. The remaining six patients either did not progress from oral hypoglycaemic agents to insulin or required stable insulin doses. Endocrine function did not improve in any patient.

Exocrine pancreatic insufficiency. Eleven patients developed exocrine insufficiency, either alone (six) or in combination with endocrine insufficiency (five), and required oral pancreatic enzymes for steatorrhoea. Nine were adequately controlled and had resolution of symptoms. In the remaining two patients, steatorrhoea persisted despite treatment. Exocrine insufficiency developed before hospital discharge in all patients as their oral intake progressed toward a normal diet. Exocrine insufficiency, once established, tended to remain stable or improve over time. Six patients were maintained on stable doses of pancreatic enzymes, whereas five were able to decrease the dose (two of whom discontinued enzyme replacement). No patient experienced worsening of exocrine insufficiency.

Extent of necrosis and pancreatic insufficiency. The estimated extent of pancreatic parenchymal necrosis in patients with normal postoperative pancreatic function was 27(7) per cent, significantly less than that in either the 11 patients who developed endocrine insufficiency alone (52(6) per cent; $P = 0.006$), the six patients with exocrine insufficiency alone (66(7) per cent; $P = 0.001$) or the five patients with both (67(11) per cent, $P = 0.01$). Differences among the three latter groups were not significant. Patients in whom endocrine insufficiency occurred during hospitalization tended to have more extensive necrosis than those in whom it occurred later (62(7) *versus* 46(9) per cent; $P = 0.1$).

Incisional hernia

Incisional hernia developed in 12 patients; nine underwent repair at a mean of 15 (range 8–24) months after discharge. Primary repair was possible in five patients; the remaining four underwent specialized soft tissue coverage (three required skin grafting and prosthetic mesh and one insertion of tissue expanders for fascia approximation). The three patients who did not undergo hernia repair included one with an intestinal–cutaneous fistula, one with recurrent pancreatitis and one who refused.

Recurrent pancreatitis and pain

Two patients developed recurrent episodes of AP requiring hospitalization that resolved with conservative treatment. The original aetiologies of NP were gallstones and ERCP; neither patient was subjected to ERCP during or after these episodes to avoid precipitating another episode of NP. Four additional patients complained of occasional abdominal pain. The original aetiologies of NP were idiopathic in two, and alcohol- and ERCP-induced in one each. During these episode(s) of recurrent abdominal pain, hyperamylasaemia was never documented and hospital care was not required. In three of the four patients the pain was mild and resolved spontaneously. In the remaining patient the pain was incapacitating with a pattern similar to that of chronic pancreatitis. This latter patient had ERCP-induced NP with 40 per cent parenchymal necrosis but did not have a similar pain pattern or clinical picture of chronic pancreatitis before ERCP.

Performance status

In four patients, the ECOG score worsened after NP. This deterioration was due to recurrent episodes of pancreatitis, recurrent abdominal pain and severe steatorrhoea in one patient each and was attributed to advanced age (93 years) in the fourth. These patients had a higher APACHE II score on admission than those with unchanged ECOG status (mean 14 *versus* 9; $P < 0.05$). Change in ECOG score did not correlate with age, length of ICU or hospital stay ($P = 1$), presence of fistula ($P = 1$), recurrent pain ($P = 0.08$), recurrent pancreatitis ($P = 0.18$), or extent of parenchymal necrosis ($P = 0.3$).

Twenty-five of the 44 patients worked before NP and three reached retirement age upon recuperation. Five of the remaining 22 patients were unable to return to work because of NP-related complications, including recurrent pancreatitis, abdominal pain and severe steatorrhoea. APACHE II score on admission tended to be higher in these patients (mean 12 *versus* 7; $P = 0{\cdot}06$).

Miscellaneous related morbidity

Partial small bowel obstruction requiring adhesiolysis 5 years after NP occurred in one patient. Two patients underwent elective cholecystectomy for symptomatic cholelithiasis; NP was alcohol-induced and gallstone-related in one each, but an extensive inflammatory reaction prevented safe cholecystectomy at the time of necrosectomy in the latter. One patient developed transient functional gastric outlet obstruction and required tube gastrostomy 3 months after NP.

Discussion

Although abnormalities in pancreatic endocrine and exocrine function during AP are known to occur[8] especially with pancreatic necrosis, long-term pancreatic function after NP has not been studied, probably because the main focus of clinical research in this disease has centred on the high mortality and immediate postoperative morbidity rates.

Pancreatic function

Pancreatic insufficiency occurred in one-half of these patients, who were followed for a mean of 5 years after operative treatment of NP. Endocrine insufficiency occurred during the acute episode in about two-thirds of the affected patients and either remained stable or worsened over time. Exocrine insufficiency occurred during the acute episode, but improved in almost half of the affected patients. Development of endocrine and/or exocrine insufficiency was associated with significantly more extensive pancreatic parenchymal necrosis.

Endocrine insufficiency is the first sign of pancreatic dysfunction to develop in 22–92 per cent of patients after treatment of NP[9–15]; overt diabetes mellitus develops in 13–54 per cent[9–11,13,14] and an additional 11–60 per cent have an abnormal glucose tolerance test[9,12,14]. The temporal relation between onset of NP and endocrine insufficiency is poorly defined. It seems reasonable that endocrine insufficiency would manifest soon after parenchymal necrosis; indeed, one of Ranson's criteria is serum glucose greater than 200 mg/dl. Although this finding was confirmed by some authors[10,13,16], others suggest that it may occur later in half[14,15] or all[12] of the patients. The latter concept is supported by this study as five of 16 patients developed endocrine insufficiency 1–8 (median 2) years after NP. However, these five patients comprised nearly half of those with endocrine insufficiency alone and tended to have less extensive necrosis, which suggests other confounding causes in this subgroup, although no specific conclusion can be drawn.

Limited and conflicting[14,15] information exists on factors possibly associated with development of endocrine insufficiency. In this study, diabetes mellitus was associated with more extensive parenchymal necrosis. Endocrine insufficiency appears more frequent after alcohol-induced rather than gallstone-induced NP (64 *versus* 22 per cent)[13,14], possibly because of pre-existing pancreatic injury in chronic alcoholics. Because alcohol-induced NP is rare in the authors' practice (five of 44) compared with others' (between 41 and 83 per cent)[9,12–15], such an association could not be evaluated.

The prevalence of exocrine insufficiency after NP documented by pancreatic function tests may be as high as 70–100 per cent[10,12,13,17,18]. Steatorrhoea, however, is less common (0–20 per cent)[11,12,14,15], while an additional 22–29 per cent of patients may complain of abdominal symptoms after fatty meals[11,14,15], but no steatorrhoea. In this study, steatorrhoea was observed in 11 of the 44 patients and in the majority (nine) was ameliorated by oral pancreatic enzymes. As in others' experience[9,13,16–18], exocrine insufficiency developed in all patients before discharge (in contrast to a substantial proportion of patients who later develop endocrine insufficiency). Exocrine insufficiency after NP as reflected in laboratory parameters of fat absorption[9,17,18] tends to improve over time[9,13,16,18]. The finding in this study that clinical steatorrhoea resolved in five of 11 patients and in the remaining six did not worsen, extends this trend from the laboratory to clinical observations. Exocrine insufficiency is related to the amount of parenchymal necrosis[12,13] and has been associated with coexistent endocrine insufficiency[14]; it seems more common after alcohol-induced NP[13].

Recurrent pancreatitis and ductal morphology

Surprisingly, in the present study recurrent episodes of pancreatitis were uncommon (two of 44 patients), although they may occur in 13–30 per cent of patients after NP[12,15,19]. Recurrent abdominal pain without hyperamylasaemia or 'dyspeptic symptoms' without steatorrhoea or typical 'pancreatic pain' may occur in an additional 10–16 per cent[9,12]. Such episodes require no hospitalization, generally resolve with diet modification and may resemble mild episodes of AP; although rare and usually self-limiting, these episodes may recur and be incapacitating, as in one of the present patients. Recurrent pancreatitis and abdominal pain seem related to the cause of NP[12,15], being more common in patients with continued alcohol abuse, possibly owing to the persistent insult to the pancreas, raising the question of whether such episodes represent an exacerbation of chronic pancreatitis, rather than recurrent AP[20,21]. In this study, such problems were rare, probably because alcohol-induced NP was uncommon.

Residual abnormalities of the ductal system resulting from NP may predispose to subsequent events. Between 46 and 53 per cent[9,13,19,22] of patients subjected to ERCP a month or more after NP have normal pancreatic ductal anatomy. Clinically insignificant ductal abnormalities, not associated with abnormal functional pancreatic tests[19], can be present in an additional 35 per cent[22]. Clinically significant ductal changes are found in only 12 per cent[22] and correlate with the severity of the initial attack[13,22]. Ductal abnormalities after alcohol-induced NP[13,23] usually remain unchanged[9,16], regardless of the normalization of exocrine function[16], in contrast to after biliary NP where they may actually improve with time[13].

Abdominal wall hernia

The incidence of incisional hernia after NP varies with operative technique. Hernias are more common after marsupialization of the lesser sac, as opposed to necrosectomy and lesser sac drainage (4–6 per cent)[10,23]. With planned repeated necrosectomy and despite attempts at delayed primary closure, hernias were observed in 12 of the present patients. Similarly, Kriwanek *et al.*[11] reported a 39 per cent incidence of 'impaired abdominal wall function', including patients with 'denervation weakness'. Such hernias may be challenging to repair because of the loss of abdominal wall from severe infection, repeated abdominal explorations and coexisting fistulas. Repair should be postponed for 6–12 months until inflammation subsides, oedema resolves, adhesions mature, and the patients' overall condition and nutritional status return to normal. Occasionally, repair using native tissues may not be possible and prosthetic material is required, as in almost half of the patients who underwent hernia repair in this study.

Performance status

Given the profound effects of NP on endocrine and exocrine function, performance status is expected to be compromised. In this study, performance status worsened in four of 44 patients owing to recurrent pancreatitis, recurrent pain or severe steatorrhoea and was related to a higher APACHE II score on admission for NP. Unfortunately, there are no good long-term studies on quality of life after NP; one group claimed an 'excellent outcome'[24] and three others suggested that 77–81 per cent of patients were in 'normal'[14] or 'good'[10,23] condition. An indirect estimate of performance status is the ability to return to work. In this study, five of 22 patients (those with higher APACHE II scores on admission) were unable to work because of NP-related complications. Others have made similar observations in that 13–25 per cent of patients retired after NP[11,14,19]. In this era of cost awareness it is encouraging to demonstrate that despite the time- and resource-consuming care required by patients with NP[25], their expected quality of life and productivity makes the aggressive and intensive treatment of NP justified and cost effective[24–26].

In summary, the long-term morbidity of NP remains high. Endocrine pancreatic insufficiency occurs in one-third of the patients, is proportional to the degree of parenchymal necrosis and tends to worsen over time. Exocrine insufficiency occurs in one-quarter of the patients, is also proportional to the extent of necrosis, but improves in one-half of cases. Recurrent pancreatitis and recurrent pain are not common, while incisional hernias can pose challenging problems. Finally, patients who recover from NP, particularly those with lower APACHE II score on admission, generally have a good functional outcome without a permanent change in quality of life after the initial convalescence.

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Surgical treatment and outcome in patients with a hepatocellular carcinoma greater than 10 cm in diameter

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Background Hepatocellular carcinoma (HCC) over 10 cm in diameter at the time of diagnosis continues to account for a number of patients undergoing hepatic resection. This study evaluated the clinicopathological features and outcome following surgery for large HCC.

Methods Forty patients with a large HCC (greater than 10 cm) (group 1) resected between 1991 and 1996 were studied retrospectively. They were compared with 245 patients who had smaller HCCs (10 cm or less) (group 2).

Results No patient in group 1 had hepatitis C infection compared with 22·9 per cent in group 2 ($P = 0{\cdot}001$). Patients in group 1 were significantly younger, had higher α-fetoprotein levels (16 750 *versus* 1864 ng/ml; $P < 0{\cdot}001$), better liver function, a higher incidence of multiple tumours (27 of 40 *versus* 42·0 per cent; $P = 0{\cdot}003$) and venous invasion (35 of 40 *versus* 52·2 per cent; $P < 0{\cdot}001$), and underwent more major resections (37 of 40 *versus* 26·5 per cent; $P < 0{\cdot}001$) than those in group 2. Morbidity and mortality rates and hospital stay were comparable in the two groups. For group 1, the 1-, 3- and 5-year disease-free survival rates were 42, 30 and 28 per cent respectively. Multiple tumours, venous invasion and impaired liver function were factors associated with recurrence.

Conclusion Large HCC had specific clinicopathological features. In selected patients, resection is safe and offers the chance of long-term disease-free survival.

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Recent advances in diagnostic imaging techniques have enhanced the detection of small tumours, many less than 3 cm in diameter. Despite this, large HCCs, with a diameter of more than 10 cm[1,2], are not infrequently encountered in clinical practice. The incidence of large HCC is especially high in younger patients, accounting for 32 per cent of resectable tumours in patients aged under 40 years[3]. Delayed diagnosis may be one explanation but the question remains whether there are specific biological features related to the development of a large HCC.

Tumour size is a major determining factor in selection of treatment for HCC. Patients with a tumour more than 3 cm in diameter are not thought suitable for percutaneous alcohol injection[4–6]. One criterion for eligibility for liver transplantation is a tumour of 5 cm or less in diameter[7]. Recently, investigators have indicated that transcatheter arterial chemoembolization rarely provides complete tumour necrosis in large tumours[8,9]. Accordingly, hepatic resection may be regarded as the only reasonable treatment option for a large HCC. However, the outcome of surgery in these patients has not been clearly demonstrated.

In this study, 40 patients who had resection of a tumour larger than 10 cm in diameter were evaluated. The clinicopathological features and outcome were compared with those in patients who had hepatic resection for a tumour with a diameter of 10 cm or less within the same interval.

Patients and methods

Between 1991 and 1996, 40 patients with a HCC larger than 10 cm underwent hepatectomy at Veterans General Hospital Taipei (group 1). These patients had the tumour tissue completely removed macroscopically; four other patients with gross residual disease were excluded from the study.

There were 35 men and five women of mean age 55 (range 20–83) years (*Table 1*). Two patients had received preoperative transcatheter arterial chemoembolization, which consisted of an injection of oily contrast medium (Lipiodol; Laboratoire Guerget, Aulnay-sous-Bois, France) mixed with 25–30 mg epirubicin hydrochloride (Pharmorubicin; Farmitalia Carlo Erba Research Laboratories, Milan, Italy), followed by injection of gelatin sponge particles (Spongostan; Ferrisan, Copenhagen, Denmark) into the hepatic artery.

Preoperative evaluation of liver function included serum biochemistry, prothrombin time and measurement of indocyanine green retention rate at 15 min[10]. Preoperative imaging for tumour staging included chest radiography, abdominal ultrasonography, computed tomography, hepatic arteriography (including indirect arterial portography) and magnetic resonance imaging, if indicated.

The operative procedures have been described elsewhere[10–12]. Intraoperative ultrasonography was performed on all patients. Thoracotomy was necessary in two patients with extensive tumour involvement of the right side of the diaphragm. In eight of 40 patients, vascular inflow was occluded at the hilum. The hepatic parenchyma was transected using either a small Kelley clamp (tissue fracture technique) or an ultrasound dissector. During parenchymal transection, attempts were made to keep a surgical margin of 1 cm or more.

After the surgical procedure, the resected specimens were examined meticulously by both surgeon and pathologist. The specimens were cut into slices approximately 10 mm thick. The macroscopic features of the tumour, including size, number, capsule formation and tumour venous invasion, were recorded. The surgical margin was measured before the specimen was fixed in 10 per cent formalin. HCC was graded for histological

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Table 1 Comparison of demographic characteristics between patients with hepatocellular carcinoma with a diameter of 10 cm or less (group 2) and greater than 10 cm (group 1)

	Group 2 ($\leq$10 cm) ($n=245$)	Group 1 ($>$10 cm) ($n=40$)
Age (years)*	60·0(12·3)	55·4(15·5)†
Sex ratio (M:F)	216:29	35:5
Smoking	120	22
Alcoholism	94	15
History of blood transfusion	41	10
Family history of HCC	33	5
Disease symptomatic	109	19
HBsAg positive	162	27
Anti-HCV positive	56	0‡
Serum AFP (ng/ml)*	1864(6964)	16 750(41 162)§
$ICGR_{15}$ (%)*	12·7(8·0)	8·7(5·6)¶
Cholesterol (mg/dl)*	161(35)	186(64)**
Albumin (g/dl)*	4·0(0·4)	3·9(0·4)
Total bilirubin (g/dl)*	1·0(0·5)	1·1(1·3)
Preoperative chemoembolization	39	2

*Values are mean(s.d.). HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; anti-HCV, antihepatitis C virus antibody; AFP, α-fetoprotein; $ICGR_{15}$, indocyanine green retention 15 min after intravenous injection (normal range 0–10 per cent). †$t=2{\cdot}14$, 283 d.f., $P=0{\cdot}033$; ‡$\chi^2=11{\cdot}4$, 1 d.f., $P=0{\cdot}001$; §$t=-5{\cdot}23$, 280 d.f., $P<0{\cdot}001$; ¶$t=2{\cdot}99$, 272 d.f., $P=0{\cdot}003$; **$t=-3{\cdot}48$, 278 d.f., $P=0{\cdot}001$ *versus* group 2

Table 2 Comparison of surgical factors between patients with hepatocellular carcinoma with a diameter of 10 cm or less (group 2) and greater than 10 cm (group 1)

	Group 2 ($\leq$10 cm) ($n=245$)	Group 1 ($>$10 cm) ($n=40$)
Operative procedure		
Major resection	65	37‡
Extended lobectomy	1	8
Lobectomy	64	29
Minor resection	180	3
Segmentectomy	72	2
Subsegmentectomy	50	0
Wedge resection	58	1
En bloc resection	67	20§
Blood loss (litres)*	2·4(2·0)	3·6(2·3)¶
Blood transfusion (litres)*	1·7(1·6)	2·7(1·8)**
Operating time (h)*	6·3(1·9)	7·3(1·9)††
Volume of drained ascites (litres)*	2·5(3·3)	3·2(3·0)
Duration of drainage (days)*	9·9(6·2)	10·2(6·9)
Patients with complications†	69 (28·2)	11 (27·5)
Death†	7 (2·9)	1 (2)
Postoperative hospital stay (days)*	15·6(11·1)	13·8(6·8)

*Values are mean(s.d.). †Values in parentheses are percentages. ‡$\chi^2=65{\cdot}12$, 1 d.f., $P<0{\cdot}001$; §$\chi^2=8{\cdot}32$, 1 d.f., $P=0{\cdot}004$; ¶$t=-3{\cdot}40$, 283 d.f., $P=0{\cdot}001$; **$t=-3{\cdot}53$, 283 d.f., $P<0{\cdot}001$; ††$t=-2{\cdot}94$, 283 d.f., $P=0{\cdot}004$ *versus* group 2

differentiation according to the Edmondson–Steiner classification[13].

DNA ploidy, analysed with fresh tissue samples, was determined with a flow cytometer (Epics Profiles; Coulter Electronics, Hialeah, Florida, USA) as described previously[14,15].

Adjuvant therapy was not used after operation. Patients were followed every 2 months with measurement of serum α-fetoprotein levels, ultrasonography, and/or computed tomography or magnetic resonance imaging. On suspicion of recurrence, angiography was carried out. Diagnosis of intrahepatic tumour recurrence was made when at least two of these investigations were positive. When recurrence was diagnosed, some patients underwent repeated resection, transcatheter arterial embolization, percutaneous ethanol injection, chemotherapy, hormone therapy or radiation therapy.

The 245 patients with a tumour of 10 cm or less in diameter who had surgery within the same interval were studied for comparison (group 2) (*Tables 1* and *2*). Clinicopathological factors and outcomes were compared between the two groups.

Statistical analysis was performed with the help of the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA)[16]. Results are expressed as mean(s.d.). Student's t test was used to compare continuous variables and the χ^2 test to compare discrete variables. Survival rates were calculated by the Kaplan–Meier method[17] and survival curves were compared with the log rank test. $P<0{\cdot}05$ was considered statistically significant.

Results

There were significant differences between patients treated for large (group 1) and small (group 2) HCC in age, hepatitis C infection rate, preoperative serum α-fetoprotein level, indocyanine green retention rate at 15 min and preoperative serum cholesterol level (*Table 1*).

A significantly higher proportion of patients in group 1 underwent major resection than in group 2 (*Table 2*). In group 1, 20 patients with tumour extending to adjacent structures underwent *en bloc* resection, including right-sided partial resection of the diaphragm (12), right adrenalectomy (three), right Gerota fascia resection (four), right hemicolectomy (one) and splenectomy (one). The proportion of patients in group 1 who underwent concomitant *en bloc* resection was significantly higher than that in group 2. Patients in group 1 had more intraoperative blood loss, a greater blood transfusion requirement and longer duration of operation. The hospital mortality rate was 2 per cent in group 1 (one patient died from hepatic failure 2 months after operation) and 2·9 per cent in group 2.

The mean(s.d.) tumour size in group 1 was 14·3(3·8) cm compared with 4·3(2·1) cm in group 2. Sixteen of 40 patients in group 1 and 115 (46·9 per cent) of 245 in group 2 had a surgical resection margin of 1·0 cm or more ($P=0{\cdot}41$). The proportion of patients in group 1 with multiple tumours (27 of 40 *versus* 42·0 per cent; $P=0{\cdot}003$) and microscopic venous invasion (35 of 40 *versus* 52·2 per cent; $P<0{\cdot}001$) was significantly higher than that in group 2. Histological evidence of cirrhosis was significantly less likely in group 1 (nine of 40 *versus* 58·7 per cent; $P<0{\cdot}001$). Tumour DNA was aneuploid in about half of patients in both groups. The proliferative capacity of the tumour part in group 1 ranged from 4·0 to 24·6 (mean(s.d.) 12·2(5·7)) per cent. Regarding the proliferative capacity of both the tumour and non-tumour parts, no significant differences were observed between the two groups.

In both groups of patients, survival was not affected by preoperative transcatheter chemoembolization. In group 1, the mean disease-free survival was 15·3 (range 1–71) months. The 1-, 3- and 5-year disease-free survival rates in group 1 were 42, 30 and 28 per cent respectively. The respective 1-, 3- and 5-year overall survival rates for group 1 were 54, 34 and 34 per cent. The 1-, 3- and 5-year disease-free survival rates in group 2 were 71·8, 45·7 and 37·1 per cent. The 1-, 3- and 5-year overall survival rates for this group were 85·6, 61·9 and 48·8 per cent respectively. The disease-free survival rate ($P=0{\cdot}033$) and

Table 3 Comparison of clinicopathological factors in patients with hepatocellular carcinoma of diameter 10 cm or less (group 2) and greater than 10 cm (group 1), with and without postoperative tumour recurrence

	Group 2 ($\leq$10 cm)		Group 1 ($>$10 cm)	
	Recurrent HCC ($n = 109$)	Recurrence free ($n = 136$)	Recurrent HCC ($n = 25$)	Recurrence free ($n = 15$)
Age (years)*	60·0(12·7)	60·2(11·9)	59·3(15·6)	53·0(15·2)
Alcoholism	41	53	9	6
HBsAg positive	75	87	18	9
Multiple tumours	62	41†	20‡	7‡
Absence of tumour capsule	59	79	11	7
Venous invasion	66§	62§	24¶	11¶
Surgical margin (cm)*	1·0(1·2)	1·3(1·2)	1·1(1·2)	1·1(1·2)
Tumour DNA aneuploid	57	68	15	5
$ICGR_{15}$ (%)*	13·6(8·0)	12·2(8·0)	10·4(6·0)**	6·0(3·4)**

*Values are mean(s.d.). HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; $ICGR_{15}$, indocyanine green retention 15 min after intravenous injection (normal range 0–10 per cent); †$\chi^2 = 17{\cdot}75$, 1 d.f., $P < 0{\cdot}001$; ‡$\chi^2 = 4{\cdot}75$, 1 d.f., $P = 0{\cdot}029$; §$\chi^2 = 5{\cdot}43$, 1 d.f., $P = 0{\cdot}02$; ¶$\chi^2 = 4{\cdot}40$, 1 d.f., $P = 0{\cdot}036$; **$t = -2{\cdot}59$, 38 d.f., $P = 0{\cdot}014$ *versus* patients with recurrence in same group

overall survival rate ($P < 0{\cdot}001$) were significantly lower in group 1. Patients in group 1 with a tumour of single nodular type had a comparable survival rate to those in group 2 ($P = 0{\cdot}589$).

Twenty-five patients in group 1 developed HCC recurrence; 16 patients received one or more additional treatments: repeated resection (one), transcatheter arterial embolization (nine), percutaneous alcohol injection (one), hormonal therapy (one), systemic chemotherapy (six) and radiation therapy (three). Similar treatments were given to the 109 patients in group 2 who developed recurrence.

Factors possibly associated with recurrent HCC were analysed. In both groups, patients with recurrent HCC had a significantly higher incidence of tumour venous invasion and multiple tumour pattern (*Table 3*). Patients in group 1 with recurrent HCC had significantly worse preoperative liver function, as reflected by a higher indocyanine green retention rate at 15 min.

Discussion

Resection of a large HCC is a surgical challenge. Although operating time and blood loss were greater, the morbidity and mortality rates in this study were comparable to those associated with resection of smaller HCC.

The principles of liver surgery for large HCC included anatomical and major resection, with preliminary ligation of the vascular inflow. In addition, the anterior approach[18], which involves initial completion of the parenchymal transection before the right hepatic lobe is mobilized, was adopted for large tumours of the right lobe, especially when there was adhesion to the diaphragm. Additional right thoracotomy was therefore not necessary. Only one of the patients in this series had postresectional hepatic failure. Extended surgical treatment was well tolerated for large HCC resection in this study because these patients had a low incidence of cirrhosis with relatively well maintained liver function. When a tumour-bearing lobe is occupied mostly by tumour tissue, deterioration of liver function after resection is mild.

Some previously reported features of large HCC observed in this study included: (1) increased frequency in young patients[3,19]; (2) high α-fetoprotein level[19,20]; (3) high incidence of venous invasion and intrahepatic metastasis[21,22]; (4) high incidence of grade III and IV disease[22]; (5) high incidence of positive resection margin[21]; and (6) high postresectional recurrence rate[21,22].

Reports concerning the correlation between DNA ploidy pattern and size of HCC have been controversial[23–29]. Nagasue *et al.*[26] indicated that aneuploidy was more frequent in larger and less differentiated HCCs. Other investigators found no significant correlation[27–29]. In the present study there was no correlation between tumour size, DNA ploidy pattern and proliferative capacity of the tumours.

None of the patients with large HCC in this study was positive for hepatitis C virus infection, in contrast to 22·9 per cent of patients with smaller HCCs. Hepatitis B surface antigen was detected equally in the two groups of patients. This variation has not been reported before. One possible explanation is that patients infected with hepatitis C virus who develop HCC are older and show more severe liver disease.

The long-term outcome of patients who have hepatectomy for large HCC is significantly compromised by the presence of residual disease at the transection line[30], despite complete removal of the tumour on gross examination. In the present series, 40 per cent of the patients with a large HCC had a surgical margin of 1 cm or more, which has been regarded as adequate for cure[31]. Performing major and anatomical resections is one way to achieve a negative histological resection margin[32]. In addition, since the incidence of tumour venous invasion is high, anatomical resection offers a chance of early extrahepatic ligation of the portal pedicle of the resected segment(s) before parenchymal transection to avoid tumour spread during manipulation.

The less favourable disease-free and overall survival rates after resection of large HCC reflect the relatively advanced stage of the disease and the difficulty in treating recurrent tumour owing to concomitant extrahepatic disease. There is a subgroup of patients with potentially less malignant large HCC, whose prognosis is not necessarily dismal (*Table 3*). Patients with a single nodular type HCC may benefit especially from resection despite the large size of the tumour.

The present study indicates that, within safety limits dictated by anatomical factors and hepatic function reserve, major resection surgery can be done safely in selected patients with a large HCC. Long-term disease-free survival can be achieved in a proportion of these patients.

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Circulating interleukin 6 concentrations and insulin resistance in patients with cancer

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Background The mechanism of insulin resistance in patients with cancer is not clear. This study was conducted to evaluate the possible role of circulating cytokines in inducing insulin resistance in patients with cancer.

Methods Twenty-three patients with a variety of cancers were studied, including one patient with oesophageal cancer, 12 with gastric cancer, four with colon cancer and six with lung cancer. Six normal volunteers served as controls. Insulin resistance was evaluated by euglycaemic hyperinsulinaemic glucose clamp with a high physiological insulin concentration of 100 μunits/ml. Metabolized glucose, the M value, was compared between patients with cancer and controls. Serum concentrations of interleukin (IL) 6 and other cytokines (tumour necrosis factor (TNF) α, IL-8 and IL-10) were measured by enzyme-linked immunosorbent assay.

Results The mean(s.d.) M value for patients with cancer (5·47(1·59) mg per kg per min) was significantly lower than that for controls (8·23(0·79) mg per kg per min) ($P < 0·001$). There was no relationship between the M value and degree of body-weight loss. Serum IL-6 concentration was measurable in eight of 23 patients: four with lung cancer, two with gastric cancer, and one each with oesophageal and colon cancer. None of the controls had a measurable serum IL-6 concentration. There was no significant relationship between serum IL-6 concentration and body-weight loss. TNF-α was undetectable in the serum of both patients with cancer and controls. Serum IL-8 and IL-10 were detected in seven and one of 23 patients respectively. These cytokines were not detected in the serum of controls. The M value was significantly smaller in those with measurable serum IL-6 (4·01(1·22) mg per kg per min) than in those with no measurable IL-6 (6·26(1·16) mg per kg per min) ($P < 0·001$). IL-6 and IL-8 levels were raised more frequently in the same patient but there was no significant relationship between IL-8 and M values.

Conclusion These results may suggest that IL-6 is related to insulin resistance in patients with cancer.

Patients with cancer often demonstrate a variety of biochemical and metabolic abnormalities. Many studies have revealed changes in glucose metabolism, including insulin resistance[1,2]. However, it was not clear whether these changes are an effect of tumour-associated malnutrition or induced by the tumour itself. In humans, insulin resistance has been shown to be a tumour-induced alteration by demonstrating reversal of the resistant state by complete removal of the tumour. Recently, it was suggested that, as a part of the inflammatory response to the presence of tumour, a variety of cytokines such as interleukin (IL) 1, IL-6 and tumour necrosis factor (TNF) α may be responsible for many of the changes in the metabolism of protein, energy and trace elements observed in cachectic patients with cancer. Considerable interest has been raised in the role of IL-6 in mediating the host response to cancer[3].

The aim of the present study was to examine the relationship between circulating cytokines and insulin resistance in patients with cancer, and to investigate the role of these cytokines in inducing insulin resistance.

Patients and methods

Patients

Twenty-three patients with a variety of cancers (15 men and eight women; mean age 62 (range 46–78) years) and six normal volunteers (two men and four women; mean age 57 (range 45–67) years) were studied. The patients included one with oesophageal cancer, 12 with gastric cancer, four with colon cancer and six with lung cancer (*Table 1*). None of the subjects had a family history of diabetes mellitus and none were taking drugs known to affect glucose metabolism. After a complete explanation of the potential risks, all subjects gave informed consent to participate in this study.

Euglycaemic glucose clamp

The subjects were studied in the morning, starting at 09.00 hours after a 12-h overnight fast. They ate a regular hospital diet, consisting of 60 per cent carbohydrate, 20 per cent protein and 20 per cent lipid (total 2000 kcal/day), without difficulty, until 1 day before the examination. During the 2-h experiment they were confined to bed rest and kept supine throughout. A computerized glucose-controlled insulin infusion system (Model STG22; Nikkiso, Tokyo, Japan) was used to analyse blood glucose levels and to infuse glucose and insulin. An 18-G catheter was inserted into the right antecubital vein and kept patent with a slow infusion of 0·9 per cent saline, containing heparin 50 units/ml. Blood samples were obtained by this route and plasma glucose levels were measured continuously by the glucose oxidase method. The contralateral arm vein was cannulated with a 20-G catheter for the infusion of insulin and glucose. A 10-min primed infusion of insulin was followed by a constant infusion of 40 munits per m^2 body surface area per min for 110 min, according to the protocol of DeFronzo *et al.* [4], which maintained the plasma insulin concentration at approximately 100 μunits/ml. Glucose was infused to maintain blood glucose at each patient's euglycaemic basal level by a built-in programmed computer system. The amount of glucose metabolized in

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Table 1 Patients examined

Patient No.	Age (years)	Sex	Site of disease	TNM stage	Body-weight loss (%)	IL-6 (pg/ml)	IL-8 (pg/ml)	M value (mg per kg per min)
1	66	M	Oesophagus	III	14·3	4·6	17·6	2·42
2	57	M	Stomach	I	0	0	0	6·42
3	62	F	Stomach	I	9·3	0	0	8·03
4	53	F	Stomach	I	0	0	0	8·86
5	63	M	Stomach	II	0	0	0	5·48
6	64	M	Stomach	II	5·0	0	0	5·44
7	46	F	Stomach	III	5·4	0	16·3	6·95
8	64	M	Stomach	III	0	0	18·3	7·24
9	75	M	Stomach	IV	25·7	0	0	5·38
10	57	F	Stomach	IV	4·0	0	0	4·90
11	64	M	Stomach	IV	10·2	0	0	5·04
12	63	M	Stomach	IV	0	3·3	14·1	4·90
13	72	M	Stomach	IV	0	6·2	0	4·56
14	46	F	Colon	III	9·0	0	0	5·48
15	59	F	Colon	III	0	0	0	6·92
16	50	M	Colon	III	0	0	0	6·03
17	57	F	Colon	IV	2·8	3·3	0	2·65
18	70	M	Lung	I	3·8	0	0	5·23
19	78	F	Lung	I	0	0	0	6·46
20	59	M	Lung	I	4·4	24·9	17·2	3·21
21	61	M	Lung	III	8·0	17·7	21·2	5·78
22	71	M	Lung	III	16·0	43·5	14·2	5·01
23	62	M	Lung	IV	13·8	15·4	0	3·53

TNM, tumour node metastasis; IL, interleukin

milligrams per kilogram body-weight per minute (M value), indicating the amount of glucose taken up by the cells, was calculated from the amount of glucose infused during the last 20 min.

Serum cytokine assay

Serum samples were obtained for each subject at the beginning of the study and stored at −70°C until assayed. IL-6 and the other cytokines (TNF-α, IL-8, IL-10 and human IL-6 soluble receptor (IL-6sR)) were measured using commercially available specific enzyme-linked immunosorbent assay (ELISA) kits (IL-6: Human IL-6 ELISA Kit Fujirebio, Fujirebio, Tokyo, Japan; TNF-α: Human TNF-α Assay Kit, Ootsuka, Tokyo, Japan; IL-8: Human IL-8 ELISA Kit, Toray-Fuji Bionics, Tokyo, Japan; IL-10: Human IL-10 ELISA Kit, Medgenix, Fleurus, Belgium; IL-6sR: Quantikine Human IL-6 sR ELISA Kit, R & D Systems, Minneapolis, Minnesota, USA). The limits of cytokine detection were 3 pg/ml (IL-6), 4 pg/ml (TNF-α), 11 pg/ml (IL-8), 14 pg/ml (IL-10) and 3·5 pg/mL (IL-6sR).

Statistical analysis

All data are expressed as mean(s.d.). Patients with cancer and controls were classified as group 1 and group 2 respectively. Statistical analysis was performed using the Mann–Whitney U test, the χ^2 test and Spearman's correlation.

Results

Fasting glucose and insulin concentrations were no different between groups 1 and 2. In both groups, plasma glucose levels were controlled at the fasting concentration throughout the period of insulin infusion. Plasma insulin was maintained at the same concentration during each examination (group 1, 103·2(27·0) μunits/ml; group 2, 99·8(30·5) μunits/ml).

M values were significantly lower in group 1 than in group 2: 5·47(1·59) and 8·23(0·79) mg per kg per min respectively ($P<0·001$). There was no significant relationship between M values and percentage body-weight loss. Data stratified by stages are shown in *Fig. 1*.

Table 2 M values, stratified by the presence and absence of raised circulating cytokine levels

	IL-6		IL-8	
	Raised ($n=8$)	Not raised ($n=15$)	Raised ($n=7$)	Not raised ($n=16$)
M value (mg per kg per min)	4·01(1·22)	6·26(1·16)*	5·07(1·79)	5·65(1·53)

Values are mean(s.d.). IL, interleukin. *$P<0·001$ *versus* raised IL-6 (Mann–Whitney U test)

IL-6 was detected in serum from eight of 23 patients, four with lung cancer, two with gastric cancer, and one patient each with oesophageal and colon cancer (*Table 1*). No IL-6 was found in serum from controls. Serum IL-6 concentration was not related to degree of body-weight loss. In patients with gastric cancer, serum IL-6 was found more frequently in patients with stage III or IV disease compared with those with stage I or II (*Fig. 2*). There was no significant relationship between serum IL-6 and either serum albumin or prealbumin concentrations. Serum levels of IL-6sR in patients with a raised level of IL-6 were no different from those seen in patients with no detectable IL-6: 35·7(8·2) and 32·8(6·7) pg/ml respectively.

No TNF-α was detected in serum from patients with cancer. IL-8 was detected in serum from seven patients in group 1. Serum IL-8 concentration was not related to the degree of body-weight loss, or serum prealbumin or albumin concentration. However, there was a measurable level of IL-8 in patients with advanced stage disease and also in one patient with stage I lung cancer (*Fig. 3*). Patients with a raised level of IL-8 more frequently had a raised level of IL-6 ($P<0·05$), so the incidence of multiple

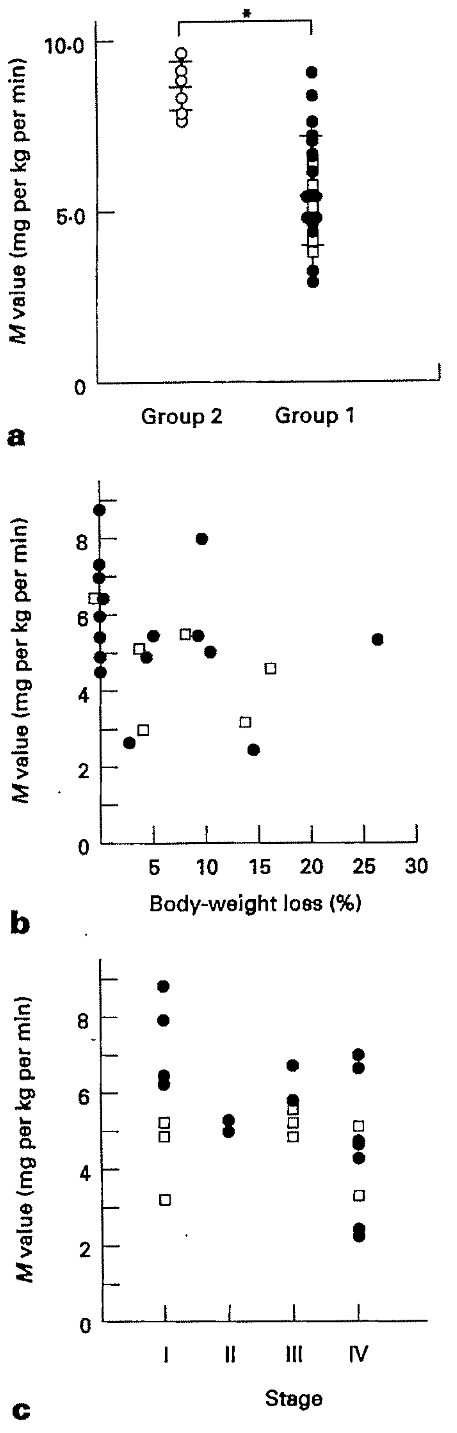

Fig. 1 a Scattergram of *M* values from controls (group 2) and patients with cancer (group 1). Bars show mean(s.d.) values. $^{*}P<0{\cdot}001$ (Mann–Whitney *U* test). b Relationship between body-weight loss and *M* value ($r_s = -0{\cdot}194$, $P = 0{\cdot}41$). c Relationship between stage of disease and *M* value. ○, Control; ●, gastrointestinal cancer; □, lung cancer

cytokine detection in an individual patient was high. IL-10 was detected in the serum from only one of 23 patients. This was a patient with a decreased *M* value and other cytokines were not detectable. None of these cytokines was detected in serum from controls.

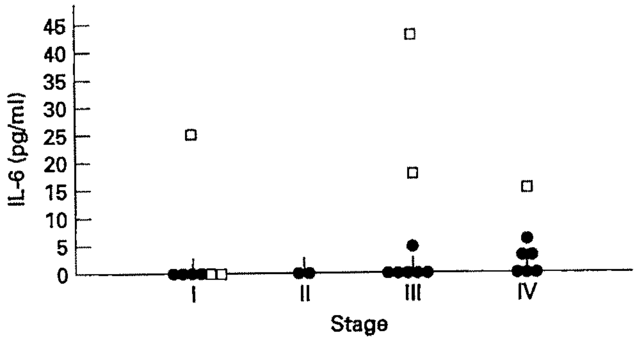

Fig. 2 Relationship between stage of disease and serum interleukin (IL) 6 concentration. ●, Gastrointestinal cancer; □, lung cancer

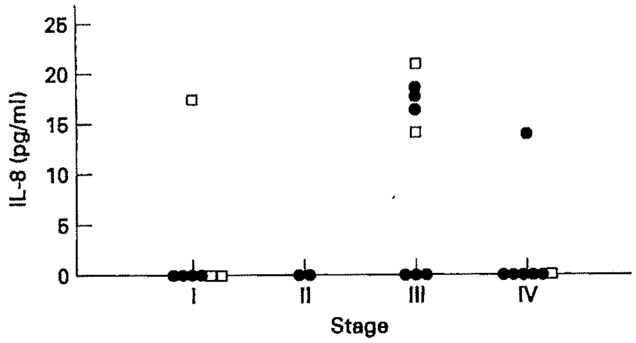

Fig. 3 Relationship between stage of disease and serum interleukin (IL) 8 concentration. ●, Gastrointestinal cancer; □, lung cancer

Table 2 shows the *M* values stratified by the presence and absence of measurable concentrations of cytokines (IL-6, IL-8). Patients with cancer and a measurable IL-6 level had a significantly lower *M* value (4·01(1·22) mg per kg per min) than those with no detectable serum IL-6 (6·26(1·16) mg per kg per min) ($P < 0{\cdot}001$). A difference in *M* value observed in patients with cancer was accounted for by those showing detectable IL-6. No relationship was found between any of the other cytokines measured and *M* value.

Discussion

Patients with cancer often demonstrate a variety of biochemical and metabolic abnormalities[5–8]. Glucose intolerance in such patients was recognized as early as in 1919[9] and has been regarded as one of the major metabolic alterations. It was reported previously that curative tumour excision resulted in recovery from insulin resistance in patients with cancer, indicating that such resistance is not caused by cancer-associated malnutrition but at least in part by the tumour itself[10]. Insulin resistance presents in patients with a variety of cancers and it is not related to the type of cancer. Although it would be ideal to select a subset of patients with the same disease, this study included patients with different diseases based on previous observations of insulin resistance. The presence of host peripheral insulin resistance could be a biological advantage to the tumour itself, enabling the tumour to draw more nutrients and to act as a 'glucose eater'.

Recently it was suggested that an individual cytokine such as IL-1, IL-6, and TNF-α may have a direct effect on glucose metabolism, forming a cytokine network *in vivo* and *in vitro* as part of the inflammatory response to tumour[11]. Furthermore, parabolic transfer of cachexia strongly suggested the presence of circulating mediators for tumour-related metabolic alterations. For this reason, serum concentrations of TNF-α and IL-6 were measured. In a further attempt to link these effects with other possible mediators, serum concentrations of IL-8, a possible mediator of cachexia, and IL-10, as an inhibitor of cytokine production[12], were measured.

IL-6 is a multifunctional cytokine with a wide range of biological activities, being associated with immune responses, the acute-phase reaction and haematopoiesis. In recent studies, measurable serum IL-6 was found in all of six patients with colonic cancer and multiple hepatic metastases[13], 24 of 45 patients with ovarian cancer[14] and 66 (48 per cent) of 138 patients with metastatic renal cell carcinoma[15]. The source of IL-6 in patients with cancer remains unknown. In some types of cancer, serum IL-6 might be produced by the cancer cells themselves and in others it might be produced by tumour-associated inflammatory cells. Strassmann and colleagues[16] reported that mice bearing colon-26 adenocarcinoma developed a profound cachexia-like syndrome. Passive immunization with anti-IL-6 monoclonal antibodies prevented the anorexia and weight loss associated with tumour growth, suggesting that IL-6 was acting as an endocrine mediator of cancer cachexia.

In this study, there was a measurable serum IL-6 level in eight of 23 patients. Those with a detectable serum level of IL-6 had a significantly lower *M* value. These results suggest a possible contribution of endogenous IL-6 production to the insulin resistance in these patients. McCall *et al.*[17] reported that patients with gastrointestinal cancer were more insulin resistant than controls and that in such patients insulin resistance correlated with serum TNF-α concentration. Furthermore, another study in rats reported that an infusion of TNF produced hepatic and peripheral insulin resistance[18]. However, in the present study, TNF-α was not detected in the serum of patients with cancer.

IL-8, also named 'neutrophil-activating protein 1', is a powerful mediator of neutrophil recruitment and activation[19]. The expression of the IL-8 gene in various cell types may be enhanced by IL-1 and TNF-α. IL-8 like IL-6 represents an important inflammatory mediator and it might be produced as part of the inflammatory response to the presence of a tumour. Ueda *et al.*[20] reported that serum IL-8 concentrations were raised in all patients with colorectal cancer and were correlated closely with serum IL-6 concentrations. In this study, serum IL-8 was detected in only seven of 23 patients and most of them also had a detectable level of IL-6. However, there was no significant relationship between IL-8 concentrations and *M* values, suggesting a different role for these cytokines with respect to insulin resistance.

IL-10 has been shown to inhibit various immune functions such as cytokine production, macrophage activation and antigen-specific T cell proliferation[12]. Gastl *et al.*[21] reported that IL-10 was released by cell lines established from a variety of solid human tumours and speculated that tumour-derived IL-10 may play a significant role in the suppression of T cell-mediated antitumour immunity. However, in the present study, serum IL-10 was detected in only one of 23 patients and did not relate to either IL-6 or IL-8 concentration.

Each cytokine exerts many biological effects, and the presence of one cytokine frequently leads to the production of another. Moreover, there is a strong duplication and synergism of actions among the cytokines through a cytokine network *in vivo*, making it difficult to determine which mediator contributes most to the disease condition. Furthermore, Corssmit *et al.*[22] demonstrated that interferon α injections given to healthy controls induced, directly or indirectly, major endocrine and metabolic changes, suggesting a possible role of the cytokine network and endocrine reactions in mediating catabolic changes to tissue injury. In this study, the *M* values of patients with a measurable serum IL-6 level were significantly decreased. The absence of TNF-α or lack of relation to IL-8 may support the role of IL-6 in inducing insulin resistance in patients with cancer. However, this relationship does not necessarily prove a cause and effect relationship. The contributions of circulating hormones, especially counter-regulatory hormones to insulin such as glucagon, cortisol[23,24] and catecholamine[25], must also be taken into account in further dissecting the mechanisms of insulin resistance in patients with cancer.

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Nitric oxide generation is increased in experimental renal warm ischaemia–reperfusion injury

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Background Nitric oxide has a clearly defined place in normal renal homoeostasis while there is a continuing debate as to its role under pathophysiological conditions. This study investigated the role of nitric oxide in a model of renal warm ischaemia–reperfusion injury.

Methods Groups of rats underwent bilateral renal warm ischaemia (for 15–60 min) followed by reperfusion (20 or 80 min) before unilateral nephrectomy for measurement of renal nitric oxide (as nitroxides) and oxidative damage. Renal function was measured on days 2 and 7 before killing and nephrectomy. A further group received the nitric oxide synthase inhibitor N^{G}-nitro L-arginine methyl ester (L-NAME; 50 mg per kg body-weight) before induction of warm ischaemia.

Results In early reperfusion there was a correlation between the duration of warm ischaemia (15–45 min) and renal nitrate ($r^2 = 0{\cdot}97$) which increased from a mean(s.e.m.) baseline value of 95(5·9) to 208(17·3) nmol per mg protein following 45 min of warm ischaemia. Levels were further raised at 80 min and maintained through to day 7 (241(12·5) nmol per mg protein in 45-min group). This rise was attenuated by L-NAME ($P < 0{\cdot}01$) as was the early rise in oxidative damage seen otherwise. By day 7, however, oxidative damage was increased (all $P \leq 0{\cdot}01$).

Conclusion Renal nitric oxide increased early in recoverable warm ischaemia–reperfusion injury and remained raised to day 7. Nitric oxide synthase inhibition ameliorated early but exacerbated late damage suggesting that the early burst of nitric oxide is cytotoxic but that overall nitric oxide may exert a cytoprotective effect.

Research has expanded dramatically over the past decade since endothelium-derived relaxing factor was first demonstrated to be nitric oxide[1]. Nitric oxide is a free radical derived from the metabolism of L-arginine[2] under the control of nitric oxide synthase (NOS). The physiological role of endothelial-derived nitric oxide in regulating vasodilatation via vascular smooth muscle cells[3] has been elucidated.

An important role for nitric oxide in renal homoeostasis has been established with both the constitutive (cNOS) and inducible (iNOS) isoforms expressed. Their distribution within the kidney varies, with cNOS predominately localized to the preglomerular vasculature, macula densa and collecting duct; iNOS is expressed more generally, with the exception of the vessels and macula densa[4]. Nitric oxide antagonizes the vasoconstrictive effect of angiotensin II on the afferent arteriole and helps regulate renal blood flow, glomerular filtration rate (GFR)[5] and sodium homoeostasis[6].

The pathophysiology following renal ischaemia–reperfusion injury is less well established. The complex, interrelated sequence of events that underlies ischaemia–reperfusion injury involves priming the endothelium during ischaemia to produce both free radicals and chemoattractants which, upon reperfusion, sequester and activate neutrophils, thus amplifying the injury[7]. There remains uncertainty about the role of nitric oxide in the postischaemic kidney and also as to when, and indeed whether, nitric oxide production is increased or depressed[8–11]. Such discrepancies highlight both the different models used (*in vitro* and *in vivo*) and the empirical nature of the conclusions, often reached by extrapolating the results of pharmacological manipulation of NOS rather than quantifying nitric oxide directly.

A new *in vivo* model was therefore devised. This allowed the collation of functional (GFR), morphological and cellular (oxidative DNA and protein damage) markers of injury with renal nitric oxide levels measured simultaneously. The changes in renal nitric oxide production following different durations of warm ischaemic damage and reperfusion are presented and, furthermore, by using the non-selective iNOS and cNOS inhibitor N^{G}-nitro L-arginine methyl ester (L-NAME) conclusions may be drawn about the role of nitric oxide in renal warm ischaemia–reperfusion injury.

Materials and methods

Materials

Unless otherwise stated all reagents were purchased from Sigma (Poole, UK).

New model of renal warm ischaemia–reperfusion injury

Studies were performed using a novel experimental model of *in vivo* renal warm ischaemia–reperfusion injury[12] (page 1669 of this issue). Briefly, groups ($n = 6$) of adult male Wistar rats (400–600 g) were anaesthetized with halothane, and the infrarenal vena cava and both renal vascular pedicles were exposed via a midline laparotomy. Twenty minutes before placing an occlusive vascular clamp across each renal pedicle, 1 ml normal saline (vehicle) was infused into the vena cava over 1 min. Following bilateral renal ischaemia (15, 30, 45 or 60 min) and reperfusion (20 or 80 min) a left nephrectomy was performed with the kidney immediately sectioned, snap frozen and stored at − 70°C until analysis. Three other groups were analysed: normal (for baseline values), sham (laparotomy, vehicle

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infusion and renal pedicle dissection without ischaemia or nephrectomy) and control (laparotomy, vehicle infusion and left nephrectomy without ischaemia). The GFR was measured on the second and seventh postoperative days using a ^{99m}Tc-diethylene triamine penta-acetic acid (DTPA) (Amersham International, Amersham, UK) clearance technique[13]. After the GFR measurement on day 7 the animal was killed; a right nephrectomy was performed immediately and part of the kidney was preserved in formalin with the remainder snap frozen. The formalin-fixed specimens were stained with haematoxylin and eosin and the damage graded on an arbitrary scale from 0 to 4 (where 0 was normal) by an experienced renal histopathologist[12].

A further group of animals was investigated using the non-selective NOS inhibitor L-NAME[14]. Twenty minutes[9] before warm ischaemia (45 min; reperfusion 20 min) vehicle containing L-NAME 50 mg/kg[8,15] was infused intravenously and the experimental protocol outlined above was followed. This group was then compared with the group subjected to 45 min of ischaemia and 20 min of reperfusion (C_{45}).

Measurement of renal nitroxides

Kidney sections were thawed on ice, weighed and homogenized with chilled (4°C) distilled, deionized water to achieve a concentration of 20 per cent w/v. The homogenates were clarified by freeze–thaw cycling[16] three times from −196°C to 4°C then centrifuged at 15000*g* for 15 min at 4°C and the supernatant decanted.

Renal nitrite was determined using an endpoint assay[17]. Equal volumes (500 μl) of homogenate and Griess reagent (BDH, Poole, UK) were mixed by vortexing and incubated at 60°C for 15 min. The absorbance of the resultant azo dye was measured spectrophotometrically and the nitrite concentration derived from a calibration curve.

Renal nitrate was calculated using a kinetic assay[18]. To a mixture of 400 μl phosphate buffer, 300 μl distilled deionized water, 250 μl homogenate, 25 μl flavin adenine dinucleotide (2·5 μmol/l final concentration) and 8 μl reduced β-nicotinamide adenine dinucleotide phosphate (96 μmol/l final concentration) was added 17 μl nitrate reductase (0·056 units). The rate of change in absorbance over 3 min at 25°C was measured spectrophotometrically (344 nm) and used to calculate the renal nitrate concentration from a calibration curve. Homogenate protein concentration was determined by the bicinchoninic acid reaction and nitrate was expressed as nmoles per milligram of protein. Two separate sections of each kidney were analysed and the mean of these readings used in subsequent analysis.

Quantification of DNA damage by high pressure liquid chromatography–electrochemical detection

The DNA was first isolated and extracted[19]. Briefly, renal samples were thawed, homogenized in extraction buffer (pH 8·0 Trisma base 0·1 mol/l, sodium chloride 0·1 mol/l, ethylenediamine tetra-acetic acid (EDTA) 20 nmol/l), centrifuged at 2500 r.p.m for 15 min at 10°C and the supernatant discarded. The pellet was resuspended (pH 8·5 Trisma base 20 mmol/l, EDTA 20 mmol/l, 1·5 per cent w/v sarkosyl and then Tris-hydrochloride 10 mmol/l, EDTA 1 mmol/l) and incubated overnight at 37°C with 250 μg ribonuclease A and 2 mg pronase E. To this was added (pH 7·5 Tris-hydrochloride 10 mmol/l, EDTA 1 mmol/l, sodium acetate 7·5 mol/l) and then the DNA was precipitated with ice-cold 100 per cent ethanol, spooled and rinsed in ethanol for 10 min. The concentration of DNA was calculated spectrophotometrically (260 nm) and aliquots (60 μg) freeze dried.

These aliquots were later reconstituted in water, heated to 100°C and rapidly cooled before digestion with nuclease P_1 (Calbiochem, Nottingham, UK) and alkaline phosphatase at 37°C. Three nucleotide standards were prepared: 2′-deoxyadenosine (dA; range 0–15 μmol/l), 2′-deoxyguanosine (dG; range 0–50 μmol/l) and 8-oxo-2′-deoxyguanosine (8-oxodG; range 0–30 nmol/l; Wako Bioproducts, Richmond, California, USA). Samples and standards were analysed on a 150 mm × 4·6 mm Hypersil ODS (C_{18}) column (Phenomenex, Macclesfield, UK) with a particle size of 3 μm. The injection loop was 100 μl with a column flow rate of 1 ml/min at ambient temperature. The dA and dG peaks were detected in the ultraviolet range (254 nm) and the 8-oxodG peak electrochemically at 800 mV (sensitivity 2 nA). System software calculated the peak areas for dA, dG and 8-oxodG in the base standards, and dG and 8-oxodG in the samples. A calibration curve for each base standard was constructed allowing the sample base concentration to be calculated (and expressed as 8-oxodG per 10^5 dG).

Quantification of carbonyl content

The carbonyl content was measured as an index of oxidative protein damage according to the method of Levine *et al*[20]. In brief, renal homogenate was mixed with 2,4-dinitrophenylhydralazine 10 mmol/l and the protein precipitated by the addition of 20 per cent w/v trichloroacetic acid. This was resuspended in guanidine 6 mol/l and the absorbance at 360 nm was determined spectrophotometrically. The carbonyl content could then be calculated using the known molar absorption coefficient (22 000 $M^{-1}cm^{-1}$) and expressed per milligram of protein.

Statistical analysis

Analysis of variance with Dunnet's comparisons was used to establish any significant difference (taken as $P<0{\cdot}05$) between the control and experimental groups with both a paired and unpaired two-tailed *t* test used where appropriate. The Kruskal–Wallis test with Dunn's comparisons was used to analyse the histological data.

Results

Survival

Eleven of 12 animals subjected to 15 min of warm ischaemia and all of those subjected to 30–60 min of warm ischaemia were alive on day 2. By day 7 survival rates were 11 of 12 (15–30 min), 10 of 12 (45 min) and two of six (60 min). With the exception of the one perioperative death all deaths occurred between days 3 and 6 (*Table 1*).

Renal nitroxides

There was no difference between the basal level of renal nitrate in the normal, sham and control groups (mean(s.e.m.) 93·3(10·8), 89·7(9·2) and 94·8(5·9) nmol per mg protein respectively). After 20 min of reperfusion nitrate had increased in all groups, significantly in the 30-min ($P<0{\cdot}05$) and 45-min ($P<0{\cdot}01$) groups compared with the control while the increase was significant (all $P<0{\cdot}05$) in all groups by 80 min of reperfusion (*Fig. 1*). There was a strong positive correlation ($r^2=0{\cdot}97$)

Table 1 Survival following renal warm ischaemia–reperfusion injury

Group	*n*	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Normal	6	6	6	6	6	6	6	6
Sham	6	6	6	6	5	5	5	5
Control	6	6	6	6	6	6	6	6
15 min	12	11	11	11	11	11	11	11
30 min	12	12	12	12	12	11	11	11
45 min	12	12	12	10	10	10	10	10
60 min	6	6	6	5	5	3	2	2
L-NAME	6	5	5	3	3	2	2	2

L-NAME, N^G-nitro L-arginine methyl ester between the duration of warm ischaemia (15–45 min) and renal nitrate at 20 min of reperfusion.

At day 7 nitrate remained significantly raised above control values ($P<0{\cdot}01$) in all groups except 60-min ischaemia. The day 7 values were also significantly higher than those of early (20 min) reperfusion in the 15- and 30-min groups ($P<0{\cdot}01$) but not in the 45- and 60-min groups. Comparison between the L-NAME group and the relevant control (C_{45}) (*Fig. 2*) demonstrated decreased renal nitrate levels at both 20 min and on day 7 ($P<0{\cdot}01$).

In none of the samples analysed was there any detectable level of nitrite.

Renal function

There was progressive impairment in the GFR at day 2, which was significant in the 30-, 45- and 60-min ischaemia groups ($P<0{\cdot}01$). By day 7 renal function had improved although it remained impaired in the 45- and 60-min groups ($P<0{\cdot}05$ and $P<0{\cdot}01$ respectively). The recovery in GFR between days 2 and 7 was significant in the 30-min ($P=0{\cdot}01$) and 45-min ($P<0{\cdot}01$) groups. There was a strong correlation between the GFR at both day 2 ($r^2=0{\cdot}88$) and day 7 ($r^2=0{\cdot}95$) and the duration of warm ischaemia[12].

Rats treated with L-NAME had impaired renal function at both day 2 ($P<0{\cdot}05$) and day 7 ($P<0{\cdot}01$) compared with those in C_{45} (*Fig. 3*).

Renal 8-oxo-2′-deoxyguanosine levels

The DNA damage increased with the duration of warm ischaemia during the early phase of reperfusion (20 min). This was significant in the 15-min ($P<0{\cdot}05$), 45-min ($P<0{\cdot}01$) and 60-min ($P<0{\cdot}05$) groups. By 80 min of reperfusion the 8-oxodG levels had returned towards control values and this persisted to day 7 (*Fig. 4*).

At 20 min of reperfusion the degree of oxidative DNA damage was significantly lower in the L-NAME group ($P<0{\cdot}01$) compared with C_{45}. By day 7, however, measured 8-oxodG was raised in the L-NAME group ($P<0{\cdot}01$) (*Fig. 5*).

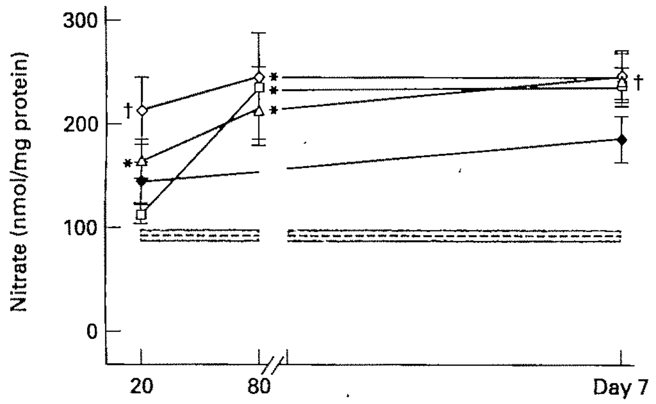

Fig. 1 Change in renal nitrate concentration during reperfusion following 15 min (□), 30 min (△), 45 min (◇) and 60 min (◆) of warm ischaemia. Values are mean(s.e.m.). Control values are denoted by dotted line (mean) and shading (s.e.m.). $^*P<0{\cdot}05$, $^†P<0{\cdot}01$ *versus* controls (analysis of variance)

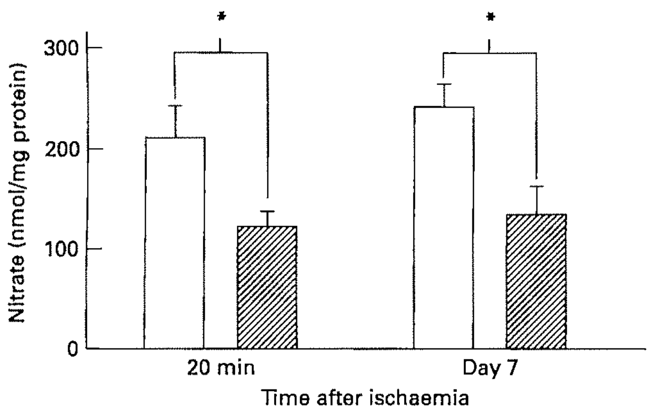

Fig. 2 Mean(s.e.m) renal nitrate concentration following 45 min of warm ischaemia with (▨) or without (□) pretreatment with the nitric oxide synthase inhibitor N^G-nitro L-arginine methyl ester. $^*P<0{\cdot}01$ (unpaired *t* test)

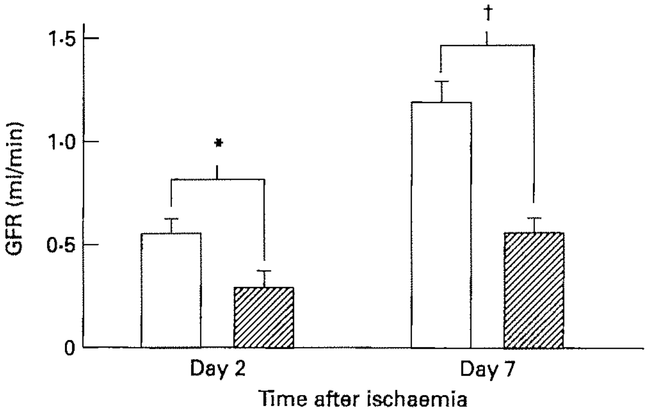

Fig. 3 Effect of the nitric oxide synthase inhibitor N^G-nitro L-arginine methyl ester (L-NAME) on postischaemic renal function. Mean(s.e.m) glomerular filtration rate (GFR) following 45 min of warm ischaemia with (▨) or without (□) L-NAME pretreatment. $^*P<0{\cdot}05$, $^†P<0{\cdot}01$ (unpaired *t* test)

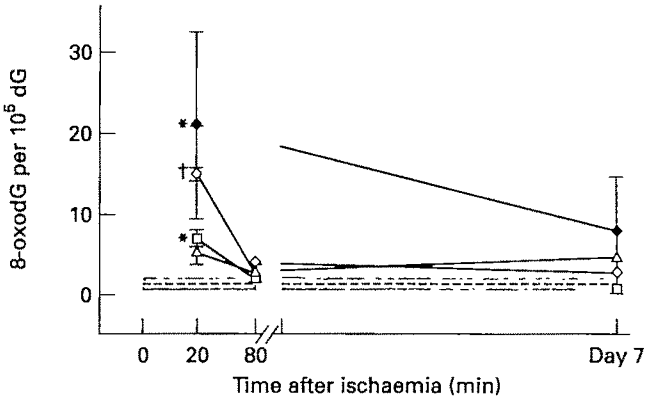

Fig. 4 Change in renal 8-oxo-2′-deoxyguanosine (8-oxodG) levels (expressed with respect to 2′-deoxyguanosine (dG)) as a marker of DNA damage during reperfusion following 15 min (□), 30 min (△), 45 min (◇) and 60 min (◆) of warm ischaemia. Values are mean(s.e.m.). Control values are denoted by dotted line (mean) and shading (s.e.m.). $^*P<0{\cdot}05$, $^†P<0{\cdot}01$ *versus* controls (analysis of variance)

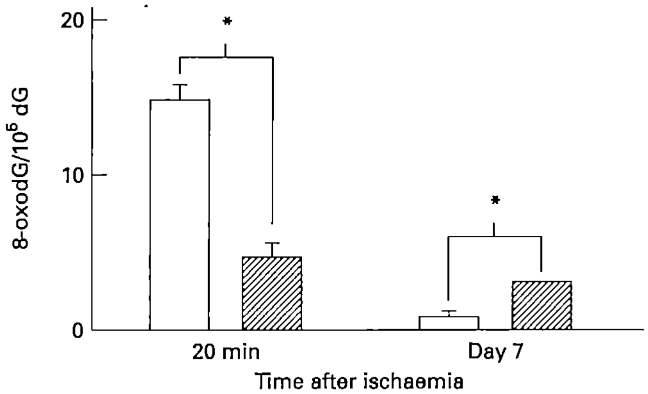

Fig. 5 Effect of the nitric oxide synthase inhibitor N^G-nitro L-arginine methyl ester (L-NAME) on postischaemic renal oxidative DNA damage. Mean(s.e.m.) renal 8-oxo-2′-deoxyguanosine (8-oxodG) levels (expressed with respect to 2′-deoxyguanosine (dG)) following 45 min of warm ischaemia with (▨) or without (☐) L-NAME pretreatment. *$P < 0{\cdot}01$ (unpaired *t* test)

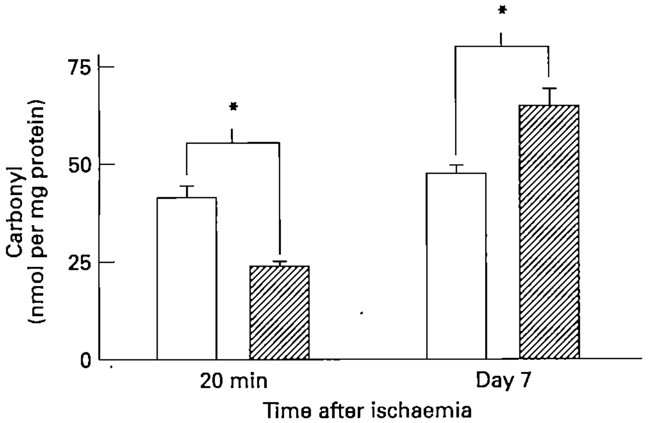

Fig. 6 Effect of the nitric oxide synthase inhibitor N^G-nitro L-arginine methyl ester (L-NAME) on postischaemic renal oxidative protein damage. Mean(s.e.m.) carbonyl content following 45 min of warm ischaemia with (▨) or without (☐) L-NAME pretreatment. *$P < 0{\cdot}01$ (unpaired *t* test)

Renal carbonyl content

The renal carbonyl content did not alter significantly from control levels at any stage of reperfusion except in the 15-min warm ischaemia group after 80 min of reperfusion ($P < 0{\cdot}01$). The carbonyl content increased from 20 to 80 min of reperfusion, significantly in the 15-min ($P < 0{\cdot}01$) and 30-min ($P = 0{\cdot}01$) groups.

At 20 min of reperfusion the carbonyl content was lower in the L-NAME group ($P < 0{\cdot}01$). By day 7 the carbonyl content was raised in the L-NAME group ($P < 0{\cdot}01$) compared with C_{45} (*Fig. 6*).

Histopathology

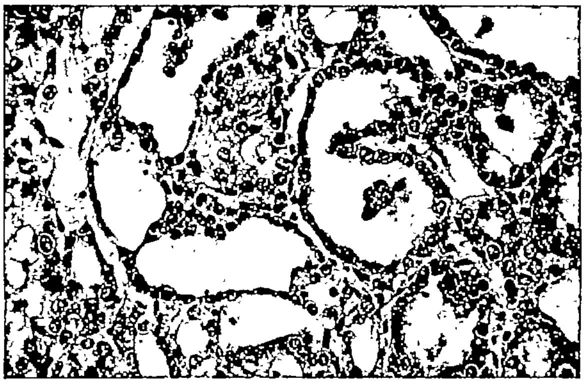

Fig. 7 Photomicrograph of renal cortical tubules 7 days after 45 min of warm ischaemia following pretreatment with N^G-nitro L-arginine methyl ester (haematoxylin and eosin stain; high power field)

Morphological damage ranged from mild (15 and 30 min of warm ischaemia) to severe (60 min) with cortical rather than medullary tubules demonstrating the most marked changes. The 60-min group alone showed areas of true necrosis with calcified tubular debris as well as mitotic figures, impaired glomerular perfusion and apoptotic/pyknotic nuclei. The most sensitive indices were the overall cortical damage and the degree of cortical tubular dilation and debris. Damage after both 45 and 60 min of ischaemia was significant ($P < 0{\cdot}01$).

There was no difference in morphology between the L-NAME (*Fig. 7*) and the C_{45} groups with respect to either cortical damage, the degree of cortical tubular dilation or debris.

Discussion

In the clinical setting renal warm ischaemia–reperfusion injury is a consequence of systemic hypoperfusion with subsequent circulatory resuscitation such as following aortic cross-clamping[21] or renal transplantation. This is especially the case in renal transplants from non-heartbeating donors which consequently have an impaired renal function[22,23].

It was important to quantify the renal nitric oxide level and compare this with cellular markers of injury at the same time as well as the functional and morphological data. Direct measurement of nitric oxide is possible[24,25] although difficult *in vivo*. While nitric oxide probes have been developed[26], their use has been restricted to *in vitro*/*ex vivo* studies. The indirect measurement of nitric oxide via the metabolites nitrate and nitrite is an established technique[17,18] for *in vivo* studies[15].

The experiments presented in this paper demonstrate that following warm ischaemia–reperfusion injury *in vivo* renal nitric oxide production is increased. The lack of measurable nitrite is unsurprising as in biological solution it is rapidly oxidized[27] to nitrate. After 20 min of reperfusion following 15–45 min of warm ischaemia, nitric oxide increased over control values by between 24 and 119 per cent respectively with a further increase at 80 min of reperfusion. There was a continued upward trend in nitric oxide levels towards day 7, reaching around 125 per cent of control values. This is comparable to the results of a model of noradrenaline-induced renal failure[10] which found NOS/nitric oxide activity maximal at 1 week. The rapid alteration in nitric oxide levels also corresponds with studies on postischaemic coronary arteries although in that bioassay nitric oxide was found to diminish with reperfusion[28].

Interestingly the generation of nitric oxide following 60 min of ischaemia did not follow this general pattern. Although levels were raised over baseline they were always lower than those in the other groups, significantly so at day 7. Whether this represents a genuine decrease in NOS activity, possibly secondary to impairment of enzyme function from the prolonged hypoxia, or more rapid quenching of nitric oxide with the other free radicals generated upon reperfusion, is not clear. The former would appear more likely as the effect continued to day 7, although *in vitro* studies have not demonstrated this effect[29]. One important conclusion from this is that models which extrapolate the results of the pharmacological manipulation of NOS to conclusions about nitric oxide generation (without quantifying nitric oxide/NOS activity) may be misleading. Furthermore, while neither urine nor serum measurements of nitrate can be used as an index of nitric oxide production in renal failure[10] this clearly is not the case for renal homogenate as the group with the most impaired renal function (60-min warm ischaemia) was associated with the lowest levels of nitrate.

It is of note that the carbonyl content was not raised above control values although this has been reported previously in cerebral homogenate[30]. It is possible that the duration of ischaemia and/or reperfusion was not sufficient to demonstrate oxidative protein damage in this model[31,32], and certainly the carbonyl content increased between 20 and 80 min of reperfusion in each group. Furthermore, the actual levels of carbonyl detected were considerably higher than those seen in plasma[33] or cerebral homogenate[34] and it is possibile that other forms of oxidative damage were being detected[20].

In this model there was a strong correlation between the duration of warm ischaemia and the functional, cellular and histological markers of renal injury, i.e. (1) the GFR at both day 2 ($r^2 = 0{\cdot}88$) and day 7 ($r^2 = 0{\cdot}95$), (2) the 8-oxodG levels at 20 min of reperfusion ($r^2 = 0{\cdot}88$) and (3) the morphology at day 7 ($r^2 = 0{\cdot}89$). These are markers of the degree of warm ischaemic damage sustained, although it would not be justified to extrapolate these results alone to reach conclusions about a causal role for nitric oxide.

When the results from pretreatment with L-NAME were analysed, however, several novel findings were apparent. Not only was nitric oxide generation decreased early in reperfusion as might be expected but this persisted through to day 7, long after the structural analogue of L-arginine had been metabolized. It was notable, however, that L-NAME did not reduce nitrate to baseline (i.e. no warm ischaemia–reperfusion injury) values. This may be due to suboptimal blockade of NOS from an inadequate dose of L-NAME or a reflection of residual iNOS activity as L-NAME may block cNOS more profoundly than iNOS[14]. Pretreatment with L-NAME further depressed renal function at both days 2 and 7 (despite similar morphological damage to C_{45}) which may be in part a reflection of the lower levels of nitric oxide and thus renal blood flow. It would appear that inhibition of NOS before induction of ischaemia impairs the long-term pathophysiological rise seen in nitric oxide. Oxidative damage to both DNA and proteins was markedly lower in the L-NAME group at the early stage of reperfusion but significantly worse by day 7. The suggestion is therefore that the raised level of nitric oxide seen early in reperfusion is injurious while later on it has a cytoprotective role. Although it would appear that the early burst of nitric oxide plays a significant role in the genesis of renal ischaemia–reperfusion injury, other pathways (free radicals, neutrophils, etc.) are clearly important. This is evident from the 60-min warm ischaemia group which demonstrated the highest levels of oxidative damage with the least increase in nitric oxide levels.

The basis for the duality of action demonstrated by nitric oxide may be hypothesized. Early in reperfusion nitric oxide is one of several free radicals generated[7] which may interact. Probably the most important of these is the rapid reaction between nitric oxide and superoxide[35] which will be cytoprotective[36] only if the product is less toxic than the constituents. The product is in fact peroxynitrite, a short-lived oxidant species that is rapidly protonated and then decays generating the highly toxic hydroxyl radical[37], thus accounting for the early cytotoxicity associated with the raised level of nitric oxide. The late cytoprotection may stem from the interaction of nitric oxide with leucocytes. The sequestration of activated neutrophils is thought to cause secondary damage[38] although it has been suggested that this is less important in the kidney than in some other organs[39,40]. Following chemotaxis, activated neutrophils adhere to the endothelium and cause injury through the release of free radicals and enzymes but all these processes are in fact inhibited by nitric oxide[41,42]. It may be therefore that the high levels of nitric oxide demonstrated in the postischaemic kidney attenuate secondary neutrophil-mediated injury[43,44] in contrast to the situation seen elsewhere (e.g. heart[28] and skeletal muscle[45]) where there is a reduction in postischaemic nitric oxide. In both modulating the effects of neutrophils and maintaining renal blood flow[46] nitric oxide may be cytoprotective in the longer term.

In summary, nitric oxide production by the post-ischaemic kidney was raised early during reperfusion and remained so for at least 7 days. Pharmacological inhibition of this increase was associated with an early (20 min) amelioration in oxidative damage but late cytotoxicity as indicated by the impaired renal function, survival and cellular markers of injury at days 2 (for GFR) and 7. Renal warm ischaemia–reperfusion injury is associated with an increase in nitric oxide production which although cytotoxic during early reperfusion has a protective role overall.

Acknowledgements

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New model of renal warm ischaemia–reperfusion injury for comparative functional, morphological and pathophysiological studies

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Background Renal warm ischaemia–reperfusion injury is pertinent to vascular and transplant surgery. While established models provide functional and morphological data the authors wanted to be able to correlate this with the underlying pathophysiology at any chosen time point, thus allowing future interventional effects on reperfusion injury to be evaluated.

Methods In a rodent model bilateral renal warm ischaemia (15–60 min) and then reperfusion (20 or 80 min) before nephrectomy allowed for analysis of early reperfusion pathophysiology. The remaining kidney provided functional data (glomerular filtration rate (GFR)) at days 2 and 7 before nephrectomy for late analysis and morphology using a new grading system.

Results Acceptable survival rate (ten of 12 animals) was seen with up to 45 min of warm ischaemia. Renal function was impaired at day 2 following 30–60 min of warm ischaemia ($P < 0.01$) and day 7 in the 45- and 60-min groups ($P < 0.05$ and $P < 0.01$ respectively). Strong correlation existed between duration of ischaemia and GFR at day 2 ($r^2 = 0.88$) and day 7 ($r^2 = 0.95$). Histological damage in the cortical tubules was evident in the 45- and 60-min groups ($P < 0.01$).

Conclusion This new model allowed comparative functional, morphological and pathophysiological studies while minimizing the number of animals required. Overall 45 min of warm ischaemia gave significant, recoverable injury and is recommended for investigating renal reperfusion injury.

Renal warm ischaemia–reperfusion injury in clinical practice is a consequence of both systemic hypoperfusion with subsequent circulatory resuscitation and local renal hypoperfusion following aortic cross-clamping or renal transplantation. The aim of these experiments was, first, to develop an *in vivo* model of renal warm ischaemia–reperfusion injury to facilitate investigation of the underlying pathophysiology and, second, to establish the ischaemic duration most suitable for use in subsequent pharmacological manipulation of the injury. Both functional (glomerular filtration rate (GFR)) and morphological parameters were measured along with the collection of renal tissue at designated time points during the ischaemia–reperfusion pathway.

The results from this study were also compared with those obtained from an established model of renal warm ischaemia–reperfusion injury. This model, by Jablonski *et al.*[1], consists of unilateral renal ischaemia followed by reperfusion and immediate contralateral nephrectomy. For the present purposes, however, the described model failed to provide both a simple, sensitive *in vivo* measurement of renal function and tissue to analyse the cellular agents and markers of reperfusion injury at any chosen time point.

Materials and methods

Animals

Adult male Wistar rats (400–600 g) were housed three to a cage and allowed free access to standard rat chow (UAR, Huntingdon, UK) and tap water. All procedures were carried out in accordance with the animal licence. Each animal underwent inhalational anaesthesia with induction and maintenance on 2 per cent halothane in oxygen and was placed on a heated mat to maintain body temperature. Some 3 ml of normal saline were injected subcutaneously into the nape of the neck to replace the ensuing losses. A midline laparotomy was performed and, using minimal dissection, both renal vascular pedicles were exposed sufficiently to allow a vascular Diffenbach clamp (Bolton Instruments, Bolton, UK) to be placed across each pedicle to occlude it.

The commencement of renal ischaemia was confirmed visually and the abdomen closed loosely over a swab moistened in sterile water. At the end of the designated warm ischaemia period (group times of 15, 30, 45 and 60 min) the abdominal pack was removed, the clamps released and reperfusion verified visually. During reperfusion (group times of 20 and 80 min) the wound edges were again apposed loosely. In the groups undergoing 80 min of reperfusion a 1-ml sample of heparinized blood was obtained with a 25-G needle from the left renal vein at different time points. At the end of the designated duration of reperfusion a left nephrectomy was performed and the kidney was weighed immediately, cut into six equal segments containing cortex and medulla and snap-frozen in liquid nitrogen. After recovery the animals were examined and weighed daily.

Control groups

Four additional groups were also investigated. A control group which underwent an identical operative procedure and nephrectomy but without renal ischaemia, a sham group which underwent an identical operative procedure with neither the renal ischaemia nor nephrectomy, and a normal group for baseline values which underwent no operative procedure. One further group was also investigated for comparison with the standard model of renal warm ischaemia[1]. This group (J_{45}) underwent an identical operative procedure except only the right renal pedicle was occluded (45 min) and following reperfusion (20 min) a left nephrectomy was performed immediately.

Assessment of renal function

Renal function was assessed on days 2 and 7 after operation using a ^{99m}Tc-labelled diethylenetriamine penta-acetate (DTPA)

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Table 1 Grades and range of parameters used to assess the degree of renal tubular damage following warm ischaemia

	Abnormality				
Parameter	Normal	Mild	Definite	Severe	With necrosis
Cortical tubules					
Epithelium	0	1	2	3	4
Dilatation	0	1	2	3	
Debris	0	1	2	3	
Nuclei	0	1	2	3	
Perfusion	0	+1/−1			
Mitoses			Count		
Apoptosis	0	1	2	3	
Medullary tubules					
Epithelium	0	1	2	3	

+1/−1, Erythrocytes present/absent

(Amersham International, High Wycombe, UK) clearance technique. Briefly, an isotope of known activity was injected into the peritoneal cavity of each animal and two accurately timed blood samples were taken via tail-tip amputation at 45 and 90 min. The plasma activity (which is dependent on renal clearance of the radioisotope) could then be quantified in a gamma counter and the GFR calculated using a slope intercept method[2,3]. By measuring two samples the inherent error in estimating the volume of distribution can be avoided.

Following the day 7 GFR measurement all animals were culled by stunning and neck dislocation and the right kidney was immediately harvested, weighed and cut into six segments containing cortex and medulla. Half of the upper pole was saved in 10 per cent neutral formalin for subsequent histological examination and the remaining tissue was snap-frozen.

Renal histopathology

The tissue preserved in formalin was batch-processed by dehydration and then embedded in paraffin. Sections were cut at 4 μm and stained with haematoxylin and eosin for histological assessment. Examination and scoring of the sections was performed on a blinded basis by an experienced renal histopathologist (P.N.F.). The slides were shuffled to avoid bias from fatigue and graded on two separate occassions (*Table 1*) with an arbitrary score of 0–4, where 0 was normal. At the first assessment the factors scored were overall cortical and medullary tubular damage, variation in nuclear shape, presence of mitotic figures and glomerular perfusion (i.e. erythrocyte count). The second assessment concentrated on cortical tubular damage which was graded for tubular dilatation, debris in the lumen of the tubules and the presence of apoptotic or pyknotic nuclei. Evidence of interstitial oedema, interstitial lymphocytic infiltration and nucleated cells marginating in the vasa recta was also sought.

Statistical analysis

Analysis of variance with Dunnet's comparisons was used to establish any significant difference (taken as $P<0\cdot05$) between the study groups with use of a paired two-tailed t test where applicable. Morphology results were analysed with the Kruskal-Wallis test with Dunn's multiple comparisons.

Results

Survival rate

At day 2, 11 of 12 animals were alive after 15 min of warm ischaemia (the one death being perioperative), 12 of 12 after 30 min, 12 of 12 after 45 min, and six of six after 60 min. At day 7 there were 11 of 12 animals surviving in the 15-min group, 11 of 12 in the 30-min group, ten of 12 in the 45-min group and two of six in the 60-min warm ischaemia group. In the J_{45} group six of six animals survived to day 7. With the exception of the one death during the perioperative period all other deaths occurred between days 3 and 6.

Renal weight

After 20 min of reperfusion, renal weight (g per kg body-weight) had increased in line with the duration of ischaemia, significantly so in the 45- and 60-min groups ($P<0\cdot05$) compared with the control group (*Fig. 1*), although by 80 min this effect had diminished. At day 7 only kidneys with either 45 min (including the J_{45} group) or 60 min of ischaemic damage were significantly heavier than the controls ($P<0\cdot01$).

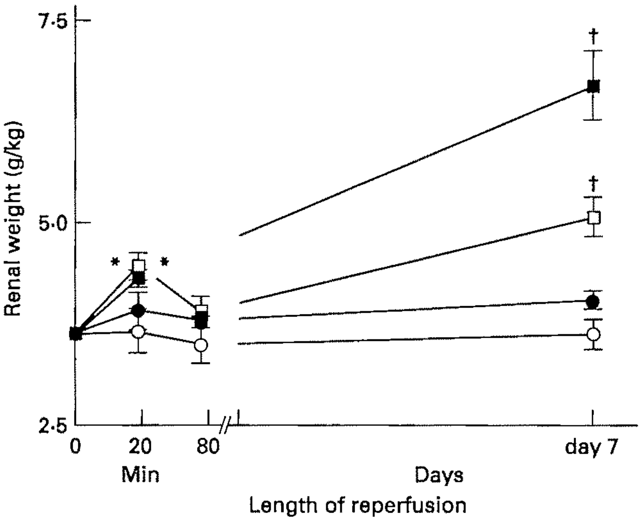

Fig. 1 Change in renal weight (g per kg body-weight) during reperfusion following a warm ischaemic insult. Warm ischaemia time: ○, 15 min; ●, 30 min; □, 45 min; ■, 60 min. Values are mean(s.e.m.). $^*P<0\cdot05$, $^†P<0\cdot01$ *versus* control (analysis of variance)

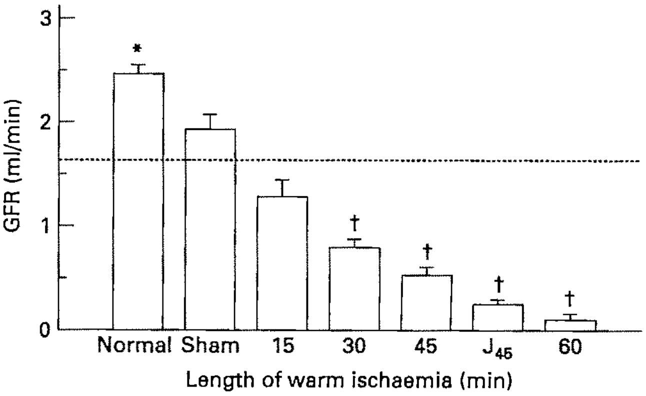

Fig. 2 Relationship between increasing renal warm ischaemia and glomerular filtration rate (GFR) at day 2. Values are mean(s.e.m.); horizontal dotted line indicates control mean value. $^*P<0\cdot05$, $^†P<0\cdot01$ *versus* control (analysis of variance)

Renal function

At day 2 there was progressive impairment in the GFR with an increasing duration of warm ischaemia (*Fig. 2*). Compared with the control this was significant in the 30-, 45- (including J_{45}) and 60-min ischaemic groups ($P < 0{\cdot}01$). The control (one kidney) GFR was also impaired when compared with the normal (two kidneys) group ($P < 0{\cdot}05$) through to day 7 ($P < 0{\cdot}01$). By day 7 there was an improvement in renal function in all the ischaemic groups although it remained impaired in the 45- (including J_{45})

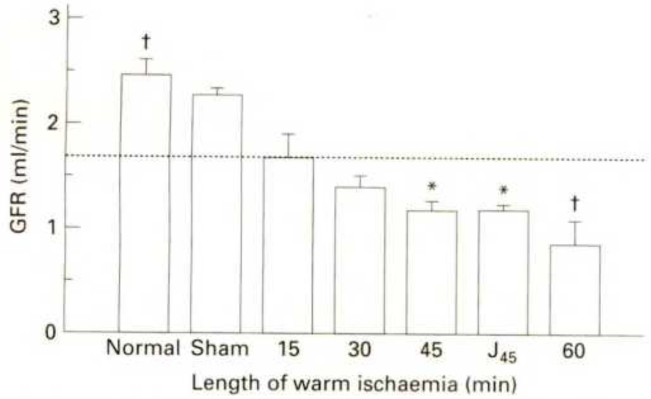

Fig. 3 Relationship between increasing renal warm ischaemia and glomerular filtration rate (GFR) at day 7. Values are mean(s.e.m.); horizontal dotted line indicates control mean value. $^*P < 0{\cdot}05$, $^\dagger P < 0{\cdot}01$ *versus* control (analysis of variance)

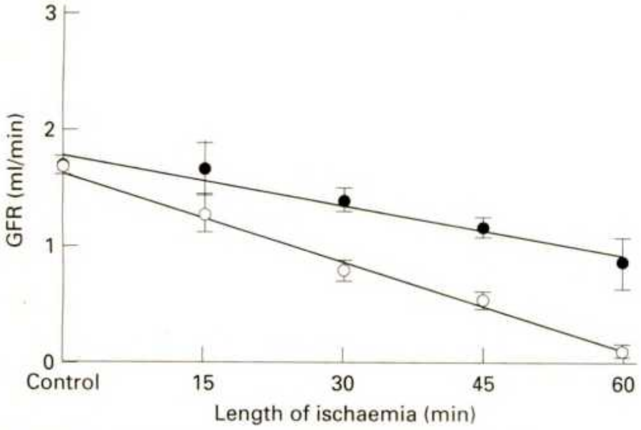

Fig. 4 Correlation between the duration of renal warm ischaemia and glomerular filtration rate (GFR) measured on day 2 (○) and day 7 (●). Values are mean(s.e.m.). At day 2 $r^2 = 0{\cdot}88$; at day 7 $r^2 = 0{\cdot}95$ (analysis of variance)

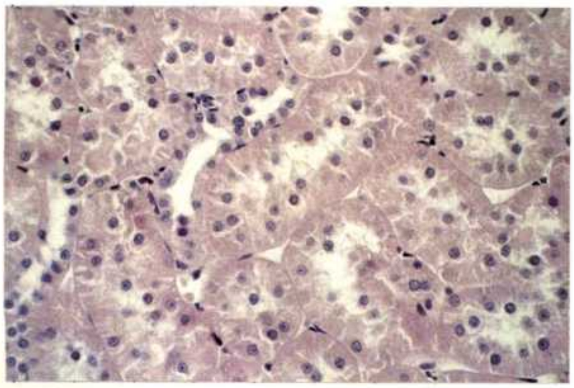

Fig. 5 Photomicrograph of rat renal cortical tubules in the control group (haematoxylin and eosin stain; high power field)

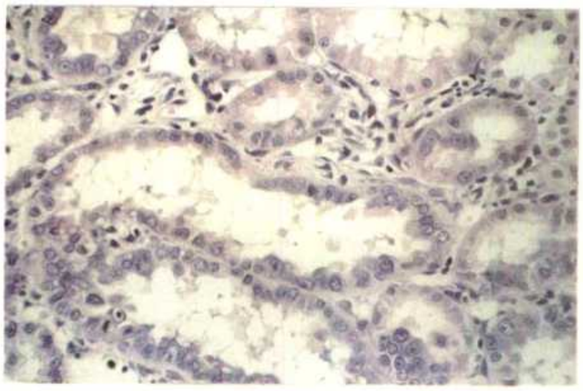

Fig. 6 Photomicrograph of rat renal cortex following 30 min of warm ischaemia showing marked tubular dilatation and debris with evidence of nuclear variation (haematoxylin and eosin stain; high power field)

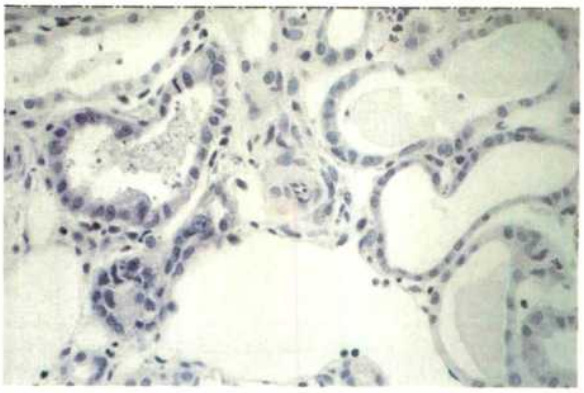

Fig. 7 Photomicrograph of rat renal cortex following 45 min of warm ischaemia showing gross tubular dilatation with debris and nuclear variation (haematoxylin and eosin stain; high power field)

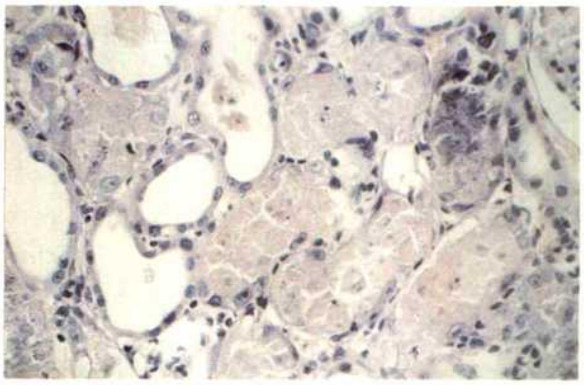

Fig. 8 Photomicrograph of rat renal cortex following 60 min of warm ischaemia, demonstrating focal necrosis along with tubular dilatation, nuclear variation and apoptosis (haematoxylin and eosin stain; high power field)

Table 2 Summary of the individual scores of renal tubular damage at day 7 in kidneys subjected to warm ischaemic injury

Ischaemic time (min)	Cortical							Medullary
	Epithelium	Dilatation	Debris	Nuclei	Perfusion	Mitoses	Apoptosis	Epithelium
15	0·58(0·45–0·73)	0·42(0·27–0·57)	0·25(0·12–0·38)	0·08(0–0·16)	0	0·17(0·06–0·28)	0	0·50(0·37–0·67)
30	1·00(0·87–1·13)	1·00(0·87–1·13)	0·73(0·54–0·92)	0·45(0·29–0·61)	0·09(0–0·18)	0	0·09(0–0·18)	0·82(0·59–1·05)
45	1·60(1·44–1·76)	1·50(1·33–1·77)	1·10(1·00–1·20)	1·10(0·92–1·28)	0	0	0	1·30(1·15–1·45)
J_{45}	1·50(1·28–1·72)	1·33(1·12–1·54)	1·33(1·12–1·54)	1·50(1·28–1·72)	−0·67(−0·46–0·88)	0·83(0·52–1·14)	0·50(0·28–0·72)	1·33(1·00–1·66)
60	3·50(3·03–4·10)	3·00	3·00	2·50(2·01–3·11)	−0·50(−0·01–1·16)	5·50(3·05–8·12)	2·50(2·04–3·23)	2·50(2·07–3·22)

Values are median (interquartile range)

and 60-min groups ($P<0·05$ and $P<0·01$ respectively) (*Fig. 3*). The recovery in GFR between days 2 and 7 was significant in the 30-min, 45-min and J_{45} groups (all $P<0·01$), but not in the 60-min group because of the excessive mortality by day 7. There was a strong correlation between GFR at day 2 ($r^2=0·88$) and day 7 ($r^2=0·95$) and the duration of warm ischaemia (*Fig. 4*).

Histopathology

Mild morphological changes were apparent in kidneys with 15 or 30 min of warm ischaemia. These changes were more pronounced after 45 min (including J_{45}) and by 60 min were severe (*Figs 5–8*). Some degree of nuclear variation was seen with increasing warm ischaemia. Overall, the cortical tubule demonstrated the most marked changes in all warm ischaemia groups, with the medullary tubule appearing relatively spared by comparison. Mitotic figures, impaired glomerular perfusion and apoptotic/pyknotic nuclei were seen only in the 60 min and J_{45} groups. The 60-min group alone showed areas of true necrosis with calcified tubular debris. Interstitial oedema, interstitial lymphocytic infiltration or nucleated cells marginating in the vasa recta were not seen in any group. Of all the factors analysed the most sensitive markers of damage were the overall assessment of cortical damage and the degree of cortical tubular dilatation and debris (*Table 2*). In these three categories, when compared with the control, both 45 and 60 min of ischaemia resulted in significant pathology (both $P<0·01$). Furthermore the 60-min group was damaged in comparison with the 15-min ($P<0·01$) and 30-min ($P<0·05$) groups. A note of caution must be raised with regard to the significance of the histological data. It could be argued that either the Fisher's exact test of χ^2 test would be preferable to Kruskal–Wallis to analyse these data. In practice, however, the numbers present in each subgroup to perform these tests were too small for any meaningful analysis.

Discussion

Renal warm ischaemia reperfusion injury in clinical practice is a sequela of both systemic hypoperfusion with subsequent circulatory resuscitation and local renal hypoperfusion following either aortic cross-clamping or renal transplantation. In abdominal aortic aneurysm (AAA) surgery the proximal extent of the neck of the aneurysm sac in relation to the renal arteries has an important bearing on subsequent morbidity and mortality. Cross-clamping the juxtarenal or suprarenal aorta is associated with an increased perioperative cardiac and pulmonary demand in addition to an ischaemic insult sustained by the kidneys and possibly the visceral organs and spinal cord. While the majority of AAA repairs allow for infrarenal cross-clamping, the consequent alteration in haemodynamics results in a significantly decreased renal blood flow[4]. Release of the aortic clamp therefore leads not only to systemic reperfusion injury[5], which will affect the kidney as a highly vascularized organ, but also a local renal reperfusion injury.

A lack of suitable organs for transplantation from traditional sources[6] has led clinicians to seek alternatives, in part from non-heart-beating donors[7]. The results are encouraging although graft survival is reduced and delayed graft function more prevalent than in kidneys from cadaveric donors. This is a consequence of the prolonged warm ischaemic insult before renal cooling can take place[8–10]. Primary non-function is also a significant problem, and a reliable preoperative test for tissue viability to prevent transplanting irrevocably damaged organs is urgently needed[11].

The experiments presented here were designed to investigate *in vivo* renal warm ischaemia–reperfusion injury exclusively. It would be a simple matter, however, to cross-clamp either the suprarenal or infrarenal aorta instead of the renal pedicles to model the more generalized warm ischaemic damage asssociated with aortic aneurysm surgery. The authors believe that this new model offers several advantages over the standard model of unilateral renal ischaemia with contralateral nephrectomy[1]. Harvesting one kidney after any chosen duration of reperfusion, as well as sampling the renal venous blood, gives access to tissue for analysis of the mechanisms of reperfusion injury such as free radicals, nitric oxide and prostanoids[12]. In addition the cellular markers of injury such as lipid peroxidation, DNA scission and protein nitrosylation can be measured and all these data correlated with the *in situ* kidney which has suffered an identical ischaemic insult. This kidney not only provides tissue to measure the same parameters after 7 days (or any other duration of reperfusion) in addition to the morphological damage, but using the simple method described allows the accurate *in vivo* quantification of renal function every second day if required[3]. A further benefit of this model lies in the potential development of a tissue viability test. Kidneys that turn out to be irrevocably damaged (equivalent to primary non-function) have an identical match in the 'perioperative' state, which can thus be used to develop a viability assay.

The measurement of GFR as the index of renal function is important as simpler estimations based on the serum creatinine and urea are too insensitive[2] and are affected by body mass and dietary factors[13]. The accuracy of the method of GFR determination described is comparable to the 'gold standard'[14] method of inulin clearance[3,15] but is considerably simpler to perform. In comparison with other radioisotope methods the short half-life (6 h) of ^{99m}Tc-labelled DTPA allows repeated GFR measurements and routine clinical disposal of contaminated waste after storage for eight half-lives (48 h). Taking two timed samples rather than a single point measure obviates the need to estimate the volume of distribution, a calculation prone to error in renal failure[16,17].

The initial intention was to score the morphological changes according to an established grading system[18] ranging from 1 (mitoses and necrosis of individual cells) to 4 (necrosis affecting all three segments of the proximal convoluted tubule). However using this system all the kidneys would have been normal or assessed as grade 1, even after 60 min warm ischaemia. There was thus a need to develop a more representative histological grading system for this model. The explanation for this discrepancy between the models probably lies in the different duration of renal recovery: 7 days in the present model and 2 days for the Jablonski model[1].

A second aim of these experiments was to determine the most useful duration of renal warm ischaemia for further studies. In this model there was good correlation between increasing warm ischaemia and the degree of renal impairment both functionally and morphologically. Altogether, an increase in warm ischaemia led to: (1) an increase in mortality rate, most marked in the 60-min group. (2) An early peak in renal weight was followed by a marked elevation at day 7. This increase must represent either hyperaemia, hypertrophy or oedema, or a combination thereof. The early peak is likely to represent reactive hyperaemia in response to the restoration of blood flow, although this cannot explain the day 7 findings. In the control group there was little evidence of hypertrophy in the remaining kidney, with an increase in mean(s.e.m.) renal weight from 1·70(0·09) g to 1·75(0·08) g over 7 days, thus excluding hypertrophy as the major cause. Oedema therefore seems most likely with pro-inflammatory cytokines known to be part of the postischaemia picture[12]. (3) A strong correlation was observed with the GFR at days 2 and 7, and (4) there were significant morphological changes, especially in the cortical tubules. Overall, 45 min of ischaemia gave rise to a significant derangement in the measured parameters while maintaining an acceptably low mortality rate. A comparison between this and the Jablonski model of 45 min of warm ischaemia showed no significant difference between the two groups in any of the measured parameters, but this new model offers the advantages already outlined. This would then be the ideal group in which to assess the efficacy of pre- or post-transplantation regimens and the effect of pharmacological manipulation of renal warm ischaemia–reperfusion injury.

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Growth rates and risk of rupture of abdominal aortic aneurysms

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Background Early identification of abdominal aortic aneurysms (AAAs) may reduce the risk of death from rupture by providing the opportunity for elective repair. Before a screening policy for AAA is implemented, the growth rates of AAAs and the accompanying risk of rupture without intervention should be established.

Methods The growth rates of AAAs were calculated using longitudinal aneurysmal growth data from screening studies in Chichester and Huntingdon. Estimates of the growth rates of AAAs and the risks of rupture over time were made taking measurement error and individual variability into account.

Results Growth rate estimates were found to vary by initial aortic diameter, with a more rapid growth seen in large aneurysms (50 mm or more). The rate of aneurysm growth did not differ with age or sex. The estimated risk of rupture of an AAA with an initial diameter of 45 mm did not exceed 20·5 per cent over 5 years. An AAA with an initial diameter of 30 mm has a 4·0 per cent or less chance of rupture over 5 years.

Conclusion The study provides a more accurate assessment of the risk of aneurysm rupture without surgery and helps to define rescreening intervals for those with an enlarged aortic diameter.

A ruptured abdominal aortic aneurysm (AAA) is responsible for approximately 1·8 per cent of all deaths in men and 0·7 per cent of all deaths in women in England and Wales[1]. In 1995, 4907 men and 1991 women died from AAA in England and Wales[2].

As the diameter of an AAA increases, so does the risk of rupture, which carries a mortality rate of up to 80 per cent, despite surgery[3–5]. AAAs can be detected with a simple and inexpensive ultrasonographic scan. Patients with a large AAA can have elective aneurysm repair, with a low risk of operative death[6–8].

A randomized controlled trial, the Multicentre Aneurysm Screening Study (MASS), is currently under way in the UK to assess the benefits of ultrasonographic screening for AAA. If screening is introduced, intervals will have to be determined for follow-up of patients with small AAAs (30–60 mm diameter). Screening intervals could be based on aneurysm growth rates and the risk of rupture associated with differing AAA diameters.

Screening has been undertaken in Chichester and Huntingdon for several years. Data are available on over 1000 individuals in whom aortic enlargement has been detected, and who have been followed up with repeated ultrasonographic measurements of the aorta. Growth curves were fitted through this series of aortic measurements and used to predict the growth of AAAs of given diameters. From the estimated growth rate, the subsequent risk of rupture of AAAs of different initial diameters could be estimated and compared with the mortality risks of elective surgery and death from other causes.

Patients and methods

Study designs and populations

The data used in this study were collected in two prospective, longitudinal, population-based screening studies in Chichester and Huntingdon. The first data set contained growth data from all individuals identified with an AAA during a series of screening studies carried out in Chichester since 1983. The protocol and 5-year results of the main study were published in a previous paper in 1995[8]. The second data set, from the Huntingdon Aneurysm Screening Project[9], began in November 1991 with the intention to screen all men aged over 50 years in the Huntingdon District. The compliance rates for all subjects included in the analyses were 76·8 per cent and 65·3 per cent for men in Huntingdon and Chichester respectively, and 73 per cent for the women from Chichester.

The follow-up protocol for the Huntingdon series was as follows: diameter 20 mm or less or patient aged more than 80 years, no further action; diameter 24 mm or less, repeat ultrasonography after 5 years; diameter 25–29 mm, repeat ultrasonography annually; diameter 30–45 mm, repeat ultrasonography every 6 months; diameter greater than 45 mm, referral to a vascular surgeon for consideration of elective repair.

The protocol for the Chichester study was: diameter 30–44 mm, repeat ultrasonography annually; diameter 45–59 mm, repeat ultrasonography every 3 months; diameter greater than 60 mm or annual growth greater than 1 cm per year or symptomatic, considered for elective repair.

Data analysis

Anteroposterior measurements of aortic diameter were used in both centres although in Chichester the larger of the anteroposterior and transverse measurements was used as the defining diameter in the primary analysis[8]. Aortic diameters of less than 30 mm were deemed normal. Individual measurements less than 30 mm were not recorded in Chichester, while in Huntingdon all diameters were recorded. Any individuals who had already undergone aortic repair were excluded from analysis.

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The data analysed from the Huntingdon study consisted of age, date and diameter for all follow-up scans. For the Chichester data set, age, sex, date and diameter of all repeat scans were available as was limited outcome data (including cause of death and type of surgery) for all members of the trial, including those who had refused to take part and the control group. A summary of the follow-up data from both centres is presented in *Table 1*. Growth data were also available from the Chichester study in a number of subjects whose AAA reached the criteria for elective surgery but who did not go on to have surgery. These patients were either unfit or refused surgery. The age of the screened individuals was defined as age at first scan. In the analyses presented here, it is assumed that aneurysm growth rates in screened subjects did not differ substantially from growth rates in those who refused to participate in the study.

The initial diameter category 50–59 mm was omitted from the Huntingdon data as there were only three subjects in this subgroup. This was due to the lower threshold for elective surgery (45 mm or more) implemented in Huntingdon. Because of the small number of individuals aged 80 years and over in the Chichester database, only men and women aged between 65 and 79 years were included in the analyses. From the Huntingdon data set, men aged between 65 and 79 years, initially screened between 21 November 1991 and 31 March 1996, were included.

Statistical analysis

Preliminary analysis and data manipulation was carried out in Stata 4.0[10]. In fitting growth curves to the longitudinal data from the Chichester and Huntingdon studies, it was assumed that the rate of growth of an AAA may vary between individuals. A 'random effects' model was used, allowing for both measurement error[11] and individual variation in growth rate[12]. In this random effects model, aortic diameter is assumed to change exponentially over time (Appendix A).

It might be the case that aneurysm growth is not continuous over time, but consists of periods of growth and periods of inactivity. However, modelling such a process explicitly is not possible owing to the limited amount of repeated observations on individuals and the degree of measurement error present. The exponential model used here can be considered to be a smoothing function for a possible underlying step-wise process. A more detailed account of the statistical analysis can be found in Appendix B.

Table 1 Summary of longitudinal data

	Chichester	Huntingdon
Subjects followed up	519	498
No. of scans		
2	89	158
3	86	121
4	91	71
5	46	45
6	49	64
7	30	19
8	32	9
9	25	8
10	15	3
11–15	37	
16–20	11	
20+	8	
Mean no. of scans	5·8	3·8
Follow-up (years)		
Up to 1	80	73
2	87	127
3	72	142
4	80	79
5	60	68
6	57	9
7	30	
8	37	
9	6	
10	3	
11	3	
12	4	
Mean follow-up (years)	3·4	2·3

Predictions of growth rates, with a known level of uncertainty, can be made over time based on a given initial diameter, or a given initial diameter and one recorded at a subsequent time point. In these predictions the second aortic measurement was taken to be 1 year later for AAAs of initial diameter 30–44 mm and 3 months later for those with a diameter of 45–59 mm. These time intervals were chosen to match the rescreening intervals implemented in the Chichester study[8] and the MASS trial. In addition to uncertainty in the estimated growth rates, an allowance was made for recorded measurements themselves being subject to a degree of uncertainty.

Associated risks of rupture over subsequent time intervals were also estimated using data on the risk of rupture according to AAA size reported by Law *et al.*[13]. This paper compiled the risk of rupture from patients with an AAA who did not undergo surgery. Thirteen follow-up studies were reported and the risk of rupture according to diameter was calculated by fitting a logistic regression model to the compiled data. Law's paper provides the best available estimates of the risk of rupture of an AAA by diameter but included only AAAs detected clinically and so AAAs detected were larger than those from a screening programme.

Results

Growth rates

The growth rate of AAAs less than 50 mm in diameter is substantially lower than the rate observed in those greater than 50 mm. Less than 0·1 per cent of 30-mm AAAs and between 0·1 and 2·4 per cent of 40-mm AAAs can be expected to have reached 60 mm within 2 years of an initial scan. This increases to between 31·3 per cent and 60·6 per cent of 50-mm AAAs, depending on their observed growth in 3 months. It is noted that 10 mm growth in 1 year is expected in less than 0·3 per cent of the population with an aneurysm.

The random effects model was applied to the data from each centre separately. The variability in growth rate between individuals can be seen in *Table 2* which shows the expected growth of AAAs over 1 year. *Table 3* shows the estimated mean growth rates of AAAs in the population by initial diameter, age and sex. *Figs 1* and *2* show the predicted growth of an AAA by initial diameter in an individual, illustrating the variation between individuals.

Figs 1 and *2* demonstrate that the increase in size of a small AAA over 5 years is expected to be small. In AAAs with a diameter exceeding 50 mm, substantial growth can be expected over time. In both Chichester and Huntingdon, the growth rate of AAAs was estimated to be slightly higher in the 75–79-year age group than in the two younger age groups (65–69, 70–74 years) which were nearly identical. No difference in AAA growth rate between men and women was observed.

Probability of exceeding 60 mm in diameter

Tables 4 and *5* record the probability that the diameter of an AAA will exceed 60 mm at some future time point, given an initial recorded diameter, or two recorded diameters taken either 1 year or 3 months apart

Table 2 Estimated percentage of aneurysms that will exceed various increases in diameter within 1 year after an initial screen

Initial diameter (mm)	Increase in diameter within 1 year (mm)					
	>0	>2	>4	>6	>8	>10
Chichester						
30	62·0	22·6	4·3	0·4	<0·1	<0·1
40	73·1	39·0	12·4	2·5	0·4	<0·1
50	94·6	73·2	31·9	7·6	1·7	0·3
Huntingdon						
25	31·4	2·0	<0·1	<0·1	<0·1	<0·1
30	40·8	14·5	3·8	0·7	0·1	<0·1
40	73·5	18·3	2·2	0·2	<0·1	<0·1

Values are estimated percentage of aneurysms

Table 3 Growth rates of aortic aneurysms by initial diameter, age and sex as estimated by a random effects model

	Estimated percentage increase in diameter per year Population mean
Chichester	
Initial diameter (mm)	
30–39	2·0 (1·1 to 2·9)
40–49	3·4 (1·6 to 5·3)
≥50	6·4 (3·8 to 8·8)
Age (years)	
65–69	2·2 (1·3 to 3·2)
70–74	3·2 (2·2 to 4·2)
75–79	2·0 (0·3 to 3·6)
Sex	
Men	3·3 (2·4 to 4·2)
Women	3·1 (0·1 to 6·0)
Huntingdon	
Initial diameter (mm)	
30–39	−1·7 (−3·1 to −0·2)
40–49	2·1 (−0·3 to 4·6)
Age (years)	
65–69	−2.0 (−3.1 to −1·0)
70–74	−1·7 (−2·8 to −0·6)
75–79	−2·2 (−3·7 to −0·8)

Values in parentheses are 95 per cent confidence intervals

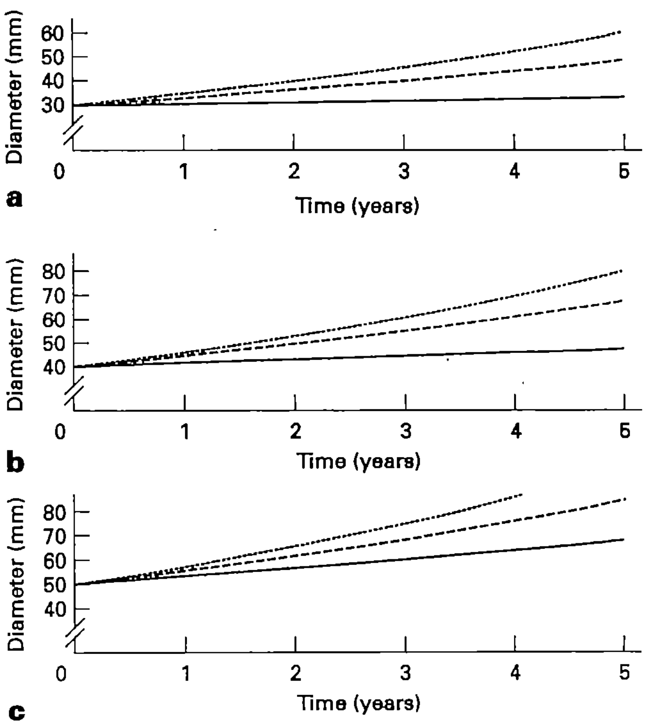

Fig. 1 Predicted growth of aneurysms with various initial diameters (a, 30 mm; b, 40 mm; c, 50 mm) as estimated from the random effects model (Chichester data). ———, median; – – – –, upper 10 per cent; ······, upper 2·5 per cent

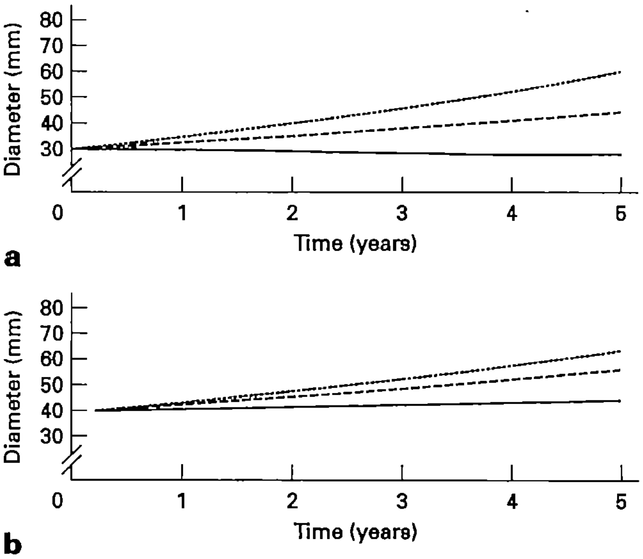

Fig. 2 Predicted growth of aneurysms with various initial diameters (a, 30 mm; b, 40 mm) as estimated from the random effects model (Huntingdon data). ———, median; – – – –, upper 10 per cent; ······, upper 2·5 per cent

(mirroring current rescreening practice in the MASS trial). For AAAs with an initial diameter less than 50 mm and 5 mm growth or less in 1 year, the probability that the diameter will increase to 60 mm, up to 3 years later, is very small. This probability increases substantially if 10 mm of growth is observed within 1 year. For an AAA with an initial diameter of 50 mm, however, even those showing no growth over a 3-month interval have a high probability (almost 50 per cent) of exceeding 60 mm 3 years later. When a diameter is measured as less than 60 mm at a particular point in time, the corresponding probability that the 'actual' diameter exceeds 60 mm is not estimated to be zero. This is because of the allowance in the model for measurement error.

Risk of rupture

Data from the Chichester and Huntingdon screening studies suggest that the probability of rupture of an AAA with an initial diameter of 30 mm, within 1 year, is very small, ranging from 0·2 to 0·4 per cent depending on diameter at first follow-up scan (*Tables 6* and *7*). This range increases to between 0·8 and 1·1 per cent for 40-mm AAAs and between 1·2 and 2·1 per cent for

Table 4 Predicted percentage of aneurysms that will exceed 60 mm at various time points after the initial screen (Chichester data)

Initial diameter (mm)	Second measurement (mm)	Time after initial screen					
		3 months	6 months	1 year	2 years	3 years	5 years
30	No measurement	<0·1	<0·1	<0·1	<0·1	0·1	2·8
	30	<0·1	<0·1	<0·1	<0·1	<0·1	0·9
	35	<0·1	<0·1	<0·1	<0·1	<0·1	4·1
	40	<0·1	<0·1	<0·1	<0·1	0·5	12·4
40	No measurement	<0·1	<0·1	0·1	0·1	5·8	20·8
	40	<0·1	<0·1	<0·1	<0·1	1·2	12·7
	45	<0·1	<0·1	<0·1	0·5	5·2	26·5
	50	<0·1	<0·1	<0·1	2·4	15·1	42·3
50	No measurement	5·8	7·8	13·5	31·3	50·3	72·1
	50	1·1	1·9	5·7	24·2	47·4	72·6
	55	4·6	7·1	15·8	42·8	63·5	81·1
	60	13·0	18·5	32·5	60·6	76·1	87·4

Values are percentage of aneurysms with a predicted diameter greater than 60 mm. Second measurements were done 1 year (30- and 40-mm aneurysms) and 3 months (50-mm aneurysms) after the initial screen

Table 5 Predicted percentage of aneurysms that will exceed 60 mm at various time points after the initial screen (Huntingdon data)

Initial diameter (mm)	Second measurement (mm)	Time after initial screen					
		3 months	6 months	1 year	2 years	3 years	5 years
30	No measurement	<0·1	<0·1	<0·1	<0·1	0·1	2·6
	30	<0·1	<0·1	<0·1	<0·1	<0·1	0·3
	35	<0·1	<0·1	<0·1	<0·1	0·1	8·6
	40	<0·1	<0·1	<0·1	<0·1	5·0	42·3
40	No measurement	<0·1	<0·1	<0·1	<0·1	0·6	5·1
	40	<0·1	<0·1	<0·1	<0·1	<0·1	2·0
	45	<0·1	<0·1	<0·1	<0·1	0·7	9·9
	50	<0·1	<0·1	<0·1	0·4	5·9	28·3

Values are predicted percentage of aneurysms with a diameter greater than 60 mm. Second measurements were done at 1 year

Table 6 Predicted percentage of aneurysms that will rupture in the 5 years after an initial screen (Chichester data)

Initial diameter (mm)	Second measurement (mm)	Time after initial screen (years)				
		1	2	3	4	5
30	No measurement	0·2	0·4	0·7	1·1	1·7
	30	0·2	0·4	0·6	0·9	1·3
	35	0·3	0·7	1·1	1·6	2·4
	40	0·4	0·8	1·4	2·4	4·0
40	No measurement	0·8	1·7	3·0	4·8	7·5
	40	0·7	1·5	2·5	3·7	5·6
	45	0·9	2·0	3·4	5·4	8·7
	50	1·1	2·5	4·5	7·9	12·9
45	No measurement	1·4	3·1	5·4	8·8	13·1
	45	1·2	2·7	4·7	7·7	11·8
	50	1·6	3·6	6·4	10·5	15·9
	55	2·1	4·8	8·6	14·0	20·5
50	No measurement	2·5	6·0	11·1	18·3	26·9
	50	2·2	5·2	9·7	16·4	25·0
	55	2·8	6·8	12·8	21·4	31·3
	60	3·6	8·8	16·5	26·6	37·7

Values are predicted percentage of aneurysms that will rupture within 1, 2, 3, 4 or 5 years after initial scan. Second measurements were done 1 year (30- and 40-mm aneurysms) and 3 months (45- and 50-mm aneurysms) after the initial screen

Table 7 Predicted percentage of aneurysms that will rupture in the 5 years after an initial screen (Huntingdon data)

Initial diameter (mm)	Second measurement (mm)	Time after initial screen (years)				
		1	2	3	4	5
30	No measurement	0·2	0·4	0·6	0·8	1·3
	30	0·2	0·4	0·6	0·8	1·0
	35	0·3	0·7	1·2	1·8	3·0
	40	0·3	0·8	1·7	3·7	8·4
40	No measurement	0·8	1·6	2·5	3·6	5·0
	40	0·7	1·5	2·4	3·3	4·4
	45	1·0	2·0	3·2	4·6	6·6
	50	1·1	2·2	4·0	6·5	10·2
45	No measurement	1·2	2·5	4·1	6·1	8·6
	45	1·1	2·3	3·8	5·6	8·0
	50	1·3	3·0	5·1	7·6	11·1
	55	2·0	4·5	7·4	11·0	15·5

Values are predicted percentage of aneurysms that will rupture within 1, 2, 3, 4 or 5 years after initial scan. Second measurements were done 1 year (30- and 40-mm aneurysms) and 3 months (45- and 50-mm aneurysms) after the initial screen

45-mm AAAs. The probability of rupture within a 5-year period after a 30-mm initial scan remains small, even when 10 mm of growth is observed in the first year. This probability is 0·04 (4·0 per cent) from the Chichester data and 0·084 (8·4 per cent) from the Huntingdon data. Ten millimetres of growth over 1 year after the initial scan occurs in the upper 1–3 per cent of a normal distribution of growth rates. Only a small percentage of the population will have such a high growth rate. Some 12·9 per cent (Chichester data) and 10·2 per cent (Huntingdon data) of these fast growing AAAs, initially with an 40-mm AAA, can be expected to rupture. The risk of rupture increases with size and thus 37·7 per cent of 50-mm AAAs that grow by 10 cm in 1 year are expected to rupture over 5 years.

Predictions from a single scan using this model will reflect the mean expected growth in the population. If more than one scan was carried out and no growth was observed during the screening interval, the predicted growth rate is estimated to be lower than the mean obtained from a single scan. Hence, the estimated risk of rupture is also lower. In contrast, an increase of 5 mm in aortic diameter between the first and second scan would indicate a higher than average growth rate, with the expectation of a higher risk of rupture in this instance.

Discussion

The Chichester and Huntingdon screening studies have provided a unique longitudinal data set on aortic growth amongst 1017 screen-detected aneurysms.

The results on the rate of growth and risk of rupture of AAAs have been presented separately for these two large data sets. This approach provides a model of aneurysm growth that allows fully for all the variability present in such data. It uses the whole sequence of aortic diameters measured over time for each individual, takes into account the possible error in the ultrasonographic measurement of aortic diameter and allows the rate of growth to vary between individuals. From the resulting estimates of growth rates, predictions of future growth and the risk of rupture for an individual can be made. There are some discrepancies between the results from the two centres, as can be seen in *Tables 2* and *3*, reflecting different follow-up protocols for AAAs less than 40 mm in diameter.

The results indicate that the rate of growth of an AAA is not influenced significantly by age. Only a slightly higher growth rate was observed among 75–79 year olds compared with those in the two younger age groups, which had nearly identical rates.

The probability of an AAA reaching a certain size, as well as the probability of rupture within the next year, was calculated using selected pairs of diameter measurements. In combination with estimated growth rates and the degree of measurement error anticipated, estimates of the risk of rupture of an AAA of given diameter could be used to devise appropriate rescreening intervals for follow-up. Screening intervals would also depend on the level of risk deemed acceptable to the population. Using the results presented here, the risk of future rupture (in the absence of surgical intervention) can now be compared directly with the risk posed by elective surgery. Thus, a patient with a 50-mm AAA, measured as 55 mm after 3 months, has only a 2·8 per cent probability that the aneurysm will rupture within the next year, compared with a commonly quoted 5 per cent mortality risk from elective surgery[6–8]. The risk that the aneurysm will rupture within 5 years is estimated at 31·3 per cent; this can also be compared with the probability of dying from all other causes over the same interval which will increase steadily with age.

The estimated probability of rupture based on an initial AAA diameter measurement alone is slightly smaller than that given in the paper by Law *et al.*[13]. This is because the risk of rupture is applied not to the measured initial diameter, but to the distribution of 'actual' diameters to which the measured diameter could correspond.

In Huntingdon, some individuals who initially had an aortic diameter of 25 mm or more had a subsequent aortic measurement of less than 25 mm and rejoined the normal group to be rescreened after 5 years. More than half the individuals screened in Huntingdon followed this pattern. This led to the spurious result that aortas of less than 40 mm decrease in diameter. At smaller diameters, observed changes in aortic diameter are largely due to measurement error and repeated measurements could be expected to regress to the mean. Patients with an initial aortic diameter of 30 mm or more in Chichester were not returned to the 'normal' pool, even if negative growth was observed, so the data do not have the same bias as those from Huntingdon.

For larger AAAs the difference in follow-up procedure has little effect, and there is striking concordance between the two centres in the estimated risk of rupture within the first 4 years (*Tables 6* and *7*). For the estimated probability of an AAA exceeding 60 mm some time in the future, the two sets of data show good agreement in the first 2–3 years of follow-up, with some of the estimates diverging at 5 years. The observation that large AAAs can be expected to grow faster than small aneurysms is consistent with the findings of other studies[14].

In this paper it was assumed that abdominal aortic aneurysms grow exponentially. When the diameters estimated by the fitted growth curves were compared with the actual observed diameters, 91·2 per cent of the observed diameters in the Chichester study and 89·9 per cent of those from the Huntingdon study differed from the fitted diameters by less than 5 mm. Some 85·8 and 96·8 per cent respectively were within 3 mm of the observed diameters. This indicated that the exponential model described the data well. However, if a linear pattern of growth was assumed, the results are very similar.

The assumption that growth rates follow a normal distribution across a population sample was examined. *Fig. 3* shows the distribution of growth rates for initial diameters of 30–39 mm and 40–49 mm in Chichester and Huntingdon. These were obtained by estimating a separate growth rate for each individual. The normality assumption appears to be reasonable, with only a few possible outlying growth rates for individuals with initial diameters of 40–49 mm in Chichester. The 'outliers' however, comprised only six individuals with a short follow-up of between 4 and 10 months compared with the mean of 38 months of follow-up in the rest. When a *t*-distribution with four degrees of freedom was used as a random effects distribution, thus allowing for the possibility of outliers, the results were very similar.

Large randomized trials are required to determine the degree of benefit, in terms of life-years gained, that might result from population screening for AAA. Modelling of the type presented here is required to determine the detailed parameters of a screening programme, such as age to start screening, frequency of rescreening and follow-up protocols for those with a small asymptomatic AAA.

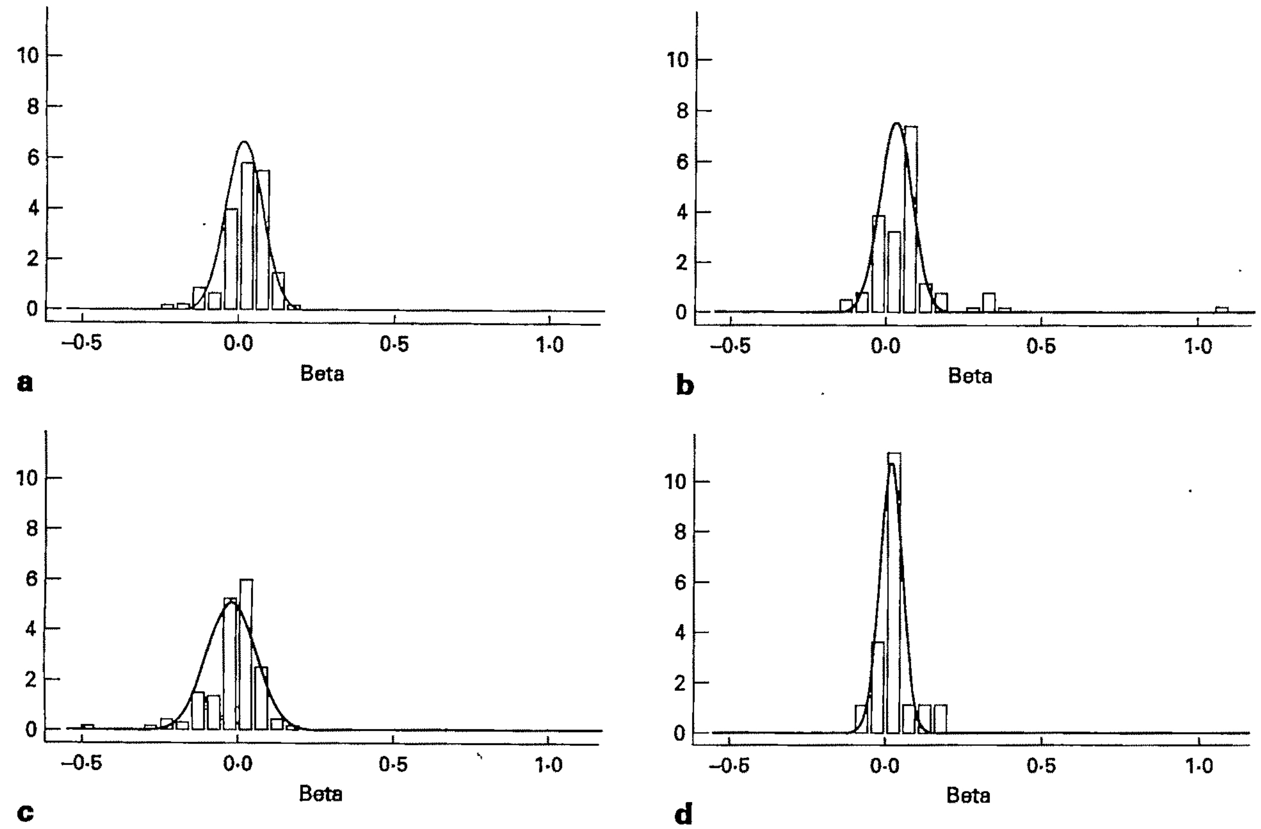

Fig. 3 Histogram of growth rates and estimated normal distribution of growth rates (———) for aneurysms with an initial diameter of 30–90 mm (a and c) or 40–49 mm (b and d) for Chichester (a and b) and Huntingdon (c and d) studies

Appendix A

Aortic diameter was assumed to change exponentially over time according to:

$$\text{Expected diameter} = \alpha \times e^{\beta t}$$

where α is the estimated initial diameter, β is the estimated coefficient and t is follow-up time (years). The exponential function ensures that absolute growth increases with diameter.

Appendix B

It has been assumed that every individual, i, in the study had his/her own growth rate, e^{β_i} and that these individual growth rates were randomly distributed about a 'mean' growth rate, e^{μ}. More specifically, the logarithms of individual growth rates in the population were assumed to be normally distributed with an unknown mean, μ, and unknown variance σ^2, i.e.

$$\beta_i \sim N(\mu, \sigma^2)$$

The variance provides an estimate of the variation of the log (growth rate) from person to person. β_i, μ and σ^2 were estimated using the whole sequence of data on diameters and years of follow-up recorded for each subject. Estimates of β_i, μ and σ^2 were obtained using Gibbs sampling[15] implemented in the BUGS software[16]. Estimates of growth rate were obtained from separate models for each centre, with μ and σ^2 being dependent on either initial diameter bands (less than 30, 30–39, 40–49, 50–59 mm) or age bands (65–69, 70–74, 75–79 years). For the Chichester data, growth rate estimates were also obtained with μ and σ^2 being dependent on sex.

The median or average growth rate was estimated by e^{μ}. The growth rate of the upper 10 per cent of the population, those with the fastest growth rate, can be obtained from μ and σ^2 by

$$e^{\mu + 1{\cdot}28\sigma}$$

where 1·28 is the upper 10 per cent value of an N(0,1) standardized normal distribution.

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No correlation between phaeochromocytoma catecholamine secretion and granule ultrastructure

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Background It is uncertain whether biochemical markers of catecholamine secretion in patients with phaeochromocytoma correlate with tumour ultrastructure granule morphology.

Methods Fifteen patients with an adrenal phaeochromocytoma ($n = 13$) or paraganglioma ($n = 2$) (three men, 12 women; age 17–79 years) were studied. Catecholamine secretion was estimated by measuring urinary levels of free noradrenaline, adrenaline and dopamine. The number and type of secretory granules were evaluated by two independent observers on electron micrographs (area analysed approximately 70 μm^2). Large round or elongated medium-density granules were adrenaline-type granules, whereas electron-dense granules lying in a vacuole were of noradrenaline type.

Results No correlation was found between noradrenaline output and the number or percentage of noradrenaline-type granules, although tumours with normal noradrenaline output had only a minority of this type of granule (less than 25 per cent). Adrenaline-type granules were predominant (77 per cent of 163 granules) in a tumour secreting only adrenaline, but the proportion of adrenaline-type granules in six tumours with normal adrenaline output varied significantly (range 7–89 per cent). It was not possible to evaluate the granule type associated with dopamine secretion because one tumour secreting 14900 nmol dopamine and 1570 nmol adrenaline daily had a predominance of noradrenaline-type granules (63 per cent of 132 granules) and two dopamine-secreting tumours (5500 and 4250 nmol per day respectively) had 93 and 13 per cent noradrenaline-type granules.

Conclusion The lack of correlation between hormone output and granularity suggests that other factors determine secretory patterns in these tumours.

In 1886, Frankel[1] described a type of adrenal tumour for which the pathologist Pick[2] proposed the name phaeochromocytoma (Greek *phaios*, dark or dusky; *chroma*, colour). Adrenaline was first identified as an active product of the adrenal medulla by Oliver and Sharpey-Schafer[3], and Stolz[4] first synthesized both adrenaline and noradrenaline. The term 'paraganglioma' is reserved for extra-adrenal catecholamine-secreting neoplasms.

The presence of two types of cell within the adrenal medulla was first identified by light microscopy based on histochemical characteristics[5]. Adrenaline-secreting cells contain a large amount of basophilic substance and stain intensely with basic dyes such as toluidine blue. Noradrenaline-secreting cells possess a strong chromaffinity, give positive iodate reactions, stain intensely with various silver impregnation methods, and exhibit weak green fluorescence after formalin fixation.

In chromaffin cells, catecholamines are stored in specific secretory granules[5]. Those with an ovoid limiting membrane, large halos and eccentrically positioned cores are noradrenaline-containing granules and measure 200–300 (range 40–1000) nm. Adrenaline granules lack the peripheral halo and the limiting membrane is closely related to the fine granular electron-dense content[6,7]. Although biochemical analysis of tumour homogenates correlate well with these morphological findings[8], others have reported that each tumour cell contains a mixed population of secretory granules[9]. A larger analysis of 50 intra- and extra-adrenal chromaffin cell neoplasms showed that 20 of 27 phaeochromocytomas contained noradrenaline granules only (three of 27 contained a mixture of noradrenaline and adrenaline granules) and 20 of 23 paragangliomas contained adrenaline-type granules only. Whether these morphological characteristics correlated with the biochemical abnormalities was not investigated[10].

Other histochemical markers for these tumours include chromogranin, synaptophysin, S100 protein and neurone-specific enolase. Their expression can be identified in the majority of phaeochromocytomas and paragangliomas[11] but this is not informative for the type of catecholamine secretion.

The secretory mechanism for catecholamines is based on their storage in secretory granules, which eventually target, dock and fuse with the plasma membrane to allow stimulus-dependent secretion[12]. The granules are, therefore, not just a storage mechanism but an obligatory step for a regulated secretory pathway. Data from *in vitro* experiments suggest that the type and number of secretory granules may determine the amount of hormone secreted. It is not known whether this can be extrapolated *in vivo*, and the aim of this study was to examine the relationship between the secretory pattern of phaeochromocytomas and the type and number of granules in tumour cells.

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Patients and methods

Fifteen patients with an adrenal phaeochromocytoma ($n = 13$) or paraganglioma ($n = 2$) were studied prospectively according to a defined protocol. There were three men and 12 women, aged between 17 and 79 (median 49) years. Clinical and biochemical data are given in *Table 1*. Urinary free catecholamine concentrations were measured by high-performance liquid chromatography. The upper limits of normal values were 800 nmol per 24 h for noradrenaline, 200 nmol per 24 h for adrenaline and 400 nmol per 24 h for dopamine. Size and weight were documented in fresh tumours in the pathology department and the anatomical position of tumours was recorded in operation notes.

Immunocytochemistry

Immunohistochemical studies were performed on selected blocks using primary antibodies against chromogranin, S100 protein and synaptophysin (DAKO, High Wycombe, UK). A standard peroxidase streptavidin–biotin complex (ABC; DAKO) method was used. S100 staining required microwave pretreatment in citrate buffer. Diaminobenzidine was used as the chromogen.

Electron microscopy

Glutaraldehyde-fixed samples were processed for electron microscopic imaging by a standard resin-embedding method. Sections were stained with lead citrate and uranyl acetate. Electron micrographs (magnification × 20 000) from four random but representative fields of each tumour (median two cells per field, total area approximately 70 μm^2) were obtained by one observer blind to the results of biochemical tests. The number and type of secretory granules on each electron micrograph were evaluated by two independent observers blind to the results of biochemical tests.

Statistical analysis

Regression analysis was performed using Excel 5-Microsoft software (Redmond, Washington, USA). The χ^2 test was used to compare results reported by the two observers evaluating the number and type of secretory granules to control for intraobserver and interobserver variance.

Results

Symptoms suggestive of excess catecholamine secretion were present in 11 patients; two patients had persistently high blood pressure. Thirteen patients had abnormally high values for at least one catecholamine measured in a 24-h urine sample (*Table 1*). The diagnosis of malignant phaeochromocytoma (two patients) was based on the development of recurrence and metastases during follow-up.

Two patients had adrenal tumours found coincidentally during imaging investigations for other conditions (incidentalomas). They had no characteristic symptoms and normal values of catecholamine excretion (*Table 1*), but histology and immunocytochemistry demonstrated catecholamine secretion and electron microscopy confirmed the presence of specific granules.

The tumours weighed between 10 and 310 (median 40, mean 76·5) g and histological examination confirmed the diagnosis of phaeochromocytoma in every case. They were composed of large pleomorphic cells, with granular cytoplasm, pleomorphic nuclei and low mitotic rates. Focal extension into the capsule and overt vascular invasion were seen in six tumours but this did not correlate with local recurrence during follow-up for up to 10 years. On immunocytochemistry the cells were strongly positive for chromogranin and sustentacular cells were positive for the S100 marker. Twelve of the 15 tumours were positive for synaptophysin.

There was no significant difference between number and type of granules evaluated by the two observers (χ^2 test for interobserver variance, $P > 0{\cdot}05$). All electron micrographs were re-examined by one observer after 4 weeks and similar results were reported (χ^2 test for intraobserver variance, $P > 0{\cdot}05$). The number of granules reported represents the sum of granules counted on four micrographs by one observer.

There was no correlation between the weight of tumours and either individual or total catecholamine secretion (calculated as the sum of noradrenaline, adrenaline and dopamine in a 24-h urine sample) (*Fig. 1*).

Table 1 Biochemical results, size of tumour and type of secretory granules in 15 patients with catecholamine-producing tumours

Patient no.	Sex	Age (years)	Diagnosis	Free noradrenaline (nmol per 24 h)*	Free adrenaline (nmol per 24 h)*	Free dopamine (nmol per 24 h)*	Tumour weight (g)	Tumour size (mm)	No. of secretory granules: Noradrenaline	No. of secretory granules: Adrenaline
1	F	25	Paraganglioma	12 880	115	5 520	82	50 × 50 × 20	87	7
2	M	64	Phaeochromocytoma	7 200	240	1 490	125	80 × 80 × 20	34	188
3	M	29	Phaeochromocytoma	6 660	677	5 790	40	55 × 45 × 35	2	23
4	F	34	Paraganglioma	6 461	27	1 654	39	55 × 40 × 40	47	9
5	M	19	Malignant phaeochromocytoma	2 570	30	< 400	175	110 × 60 × 50	6	49
6	F	49	Phaeochromocytoma	3 900	56	< 400	79	75 × 75 × 50	36	46
7	F	51	Phaeochromocytoma	2 309	27	< 400	11	25 × 20 × 20	30	96
8	F	37	Phaeochromocytoma	1 820	110	< 400	40	50 × 45 × 40	90	30
9	F	29	Phaeochromocytoma	1 693	49	4 236	10	60 × 35 × 10	34	223
10	F	17	Phaeochromocytoma	614	1 571	14 916	112	65 × 60 × 60	83	49
11	F	59	Phaeochromocytoma	603	203	1 477	15	30 × 30 × 20	40	108
12	F	69	Phaeochromocytoma	587	504	< 400	40	45 × 40 × 35	38	125
13	F	56	Malignant phaeochromocytoma	119	18	746	65	50 × 40 × 35	54	24
14	F	79	Non-functional phaeochromocytoma	775	147	< 400	154	90 × 70 × 60	6	166
15	F	49	Non-functional phaeochromocytoma	389	21	< 400	310	10 × 90 × 70	4	95

*Upper limit of normal value: 800 nmol per 24 h for noradrenaline, 200 nmol per 24 h for adrenaline and 400 nmol per 24 h for dopamine

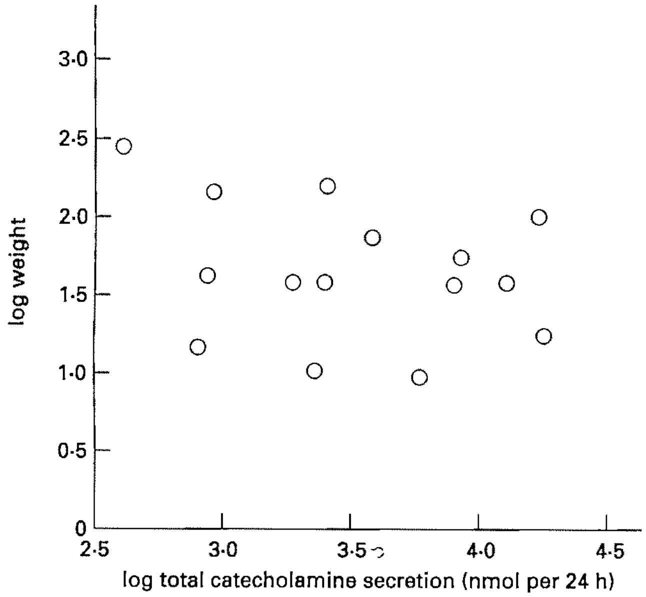

Fig. 1 Relationship between catecholamine secretion and tumour weight in 15 patients with phaeochromocytoma or paraganglioma

The number of each type of granule (percentage of the total) and the biochemical markers were not significantly correlated (*Fig. 2*). Tumours with normal noradrenaline output had few noradrenaline-type granules (mean (range) 31·4 (3·4–69·0) per cent, median 25 per cent) but the proportion of adrenaline granules in six tumours with very low adrenaline output (<50 nmol per 24 h) varied significantly (range 7–89 per cent). Adrenaline-containing granules were predominant (77 per cent of 163 granules) in a tumour secreting only adrenaline.

One of the malignant phaeochromocytomas secreted large amounts of noradrenaline (2570 nmol per 24 h), yet adrenaline granules were predominant (89 per cent of 55 granules) (*Fig. 3*).

Cells of the two 'non-functional phaeochromocytomas' (incidentalomas) contained a high number of secretory granules, predominantly of adrenaline type (more than 90 per cent), yet it was not possible to identify an excess secretion of any catecholamine.

It was not possible to evaluate the type of granule associated with dopamine secretion because a tumour secreting excessive amounts of dopamine (14 900 nmol per day) and adrenaline (1570 nmol per day) had a predominance of noradrenaline-type granules (63 per cent of 132 granules), while in two other dopamine-secreting tumours (approximately 5520 and 4236 nmol per day) noradrenaline granules represented 93 and 13 per cent respectively.

Discussion

Haematoxylin–eosin staining and immunocytochemistry for chromogranin, synaptophysin and S100 markers were used to demonstrate the neuroendocrine origin of adrenal tumours in this study. Although the presence of cells positive for S100 protein is reported to suggest a good prognosis[13], both malignant tumours from this series contained such cells. Immunohistochemical methods, however, cannot estimate the type of catecholamine produced by the tumour cells but prompted further studies using electron microscopy. For example, in the two patients with adrenal incidentalomas the values for 24-h catecholamine excretion were normal on repeated testing but the identification of cells positive for chromogranin and synaptophysin prompted electron microscopic studies. These demonstrated specific catecholamine-containing secretory granules and the tumours were therefore classified as 'non-functional phaeochromocytomas'.

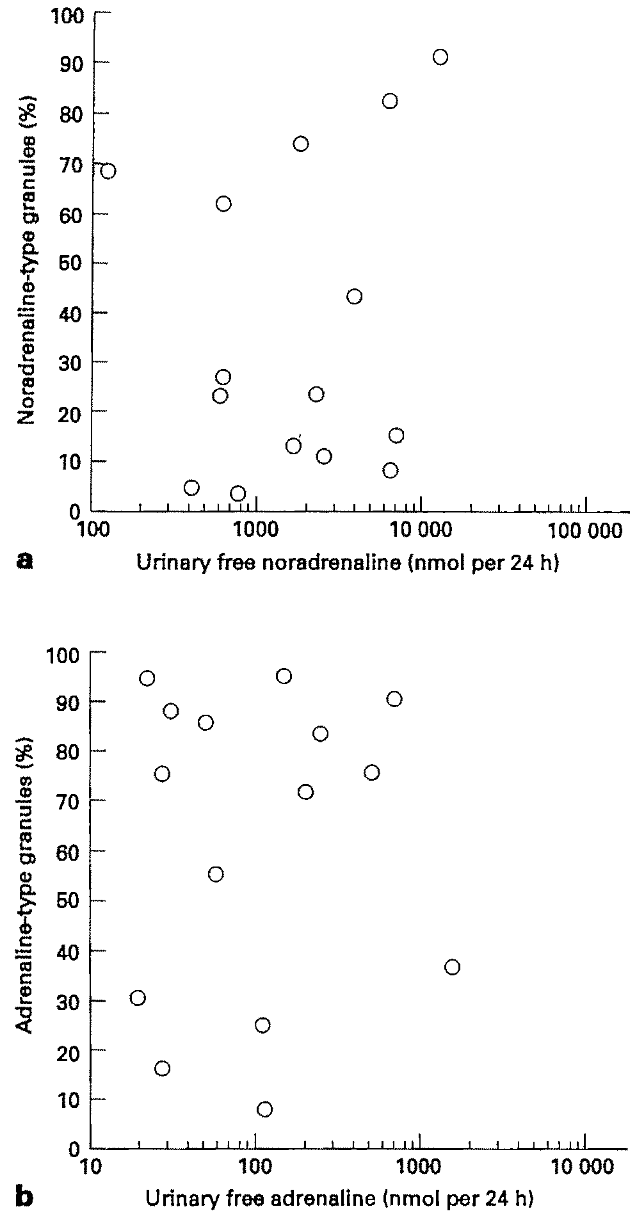

Fig. 2 Relationship between biochemical markers and type of granules in 13 patients with catecholamine-secreting tumours

Recently, direct measurement of urinary levels of free catecholamines has become the preferred method of diagnosis because it has higher diagnostic specificity and sensitivity (99·5 and 100 per cent respectively)[14] compared with the urinary concentrations of catecholamine metabolites[15]. Although in a previous study the log of tumour mass was significantly correlated with the log of

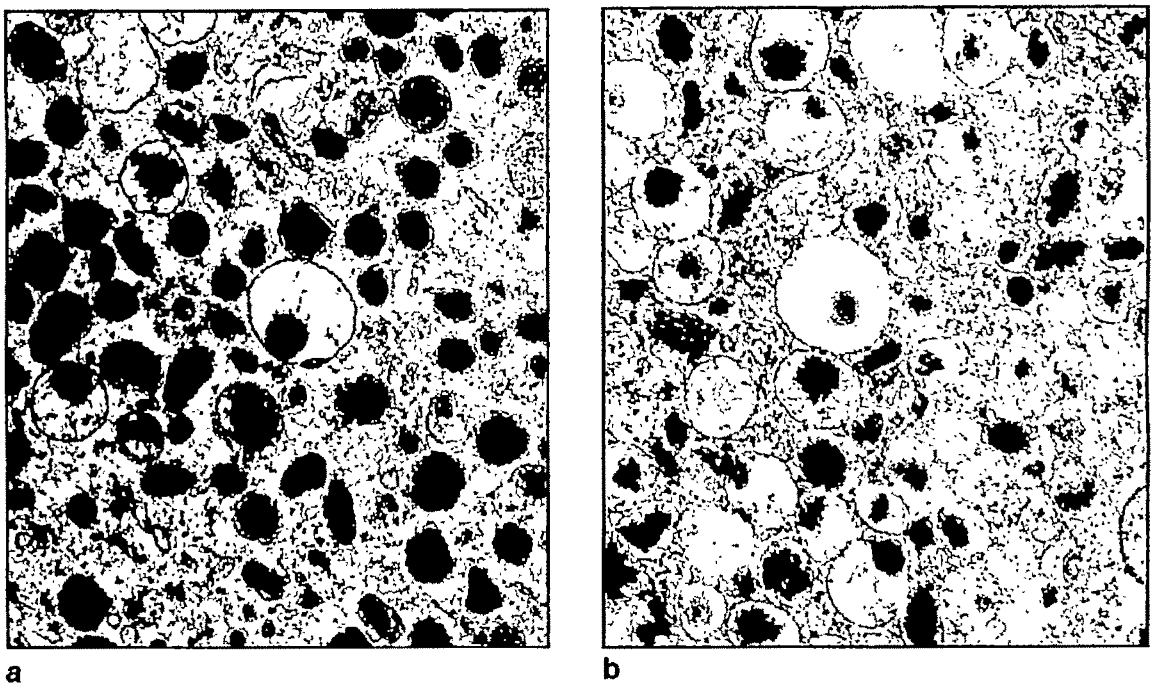

Fig. 3 Electron micrographs of representative areas (3·5 × 4·5 μm) from two phaeochomocytomas. a Predominance of adrenaline-type granules (total of 188 adrenaline *versus* 34 noradrenaline granules on four random fields) in a tumour removed from a patient secreting 7200 nmol free noradrenaline, 240 nmol free adrenaline and 1490 nmol free dopamine per 24 h. b Predominance of noradrenaline-type granules (total 90 noradrenaline *versus* 30 adrenaline granules on four random tests) in a tumour removed from a patient secreting 1820 nmol free noradrenaline, 110 nmol free adrenaline and less than 400 nmol free dopamine per 24 h

24-h urinary excretion of vanillylmandelic acid[16], no correlation was found in this group of patients between the tumour size and weight and the amount of free catecholamine excreted per 24 h (*Fig. 1*). This discrepancy could be due to internal metabolism of catecholamines in large tumours[17]. The majority of tumours in this study were large (12 of 15 tumours weighed over 30 g) and therefore most of the catecholamines would be metabolized and the amount of free catecholamine excreted in the urine would not be an exact measure of output. The difference between total tumour mass and functional or secretory mass (e.g. cystic changes) could also contribute to a lack of correlation between tumour size and catecholamine output.

Electron microscopy provides an accurate method for characterizing the morphology of secretory granules in phaeochromocytomas[6,7]. It is not practical, however, to sample vast areas, and so representative sections of a tumour are usually analysed. This may introduce a bias and, although the method offers good detail of a limited area of the tumour (restricted to several cells), it might not provide a precise overall estimate. Despite this limitation, electron microscopy remains the most accurate method for describing the type of secretory granules in phaeochromocytomas.

There was no correlation between the percentage of each type of granule and the amount of adrenaline and noradrenaline secreted. The presence of both types of granule in tumours removed from patients showing excessive secretion of only one catecholamine (noradrenaline or adrenaline) represents an important, although unexpected, finding. Normal adrenal medullary cells secrete mainly adrenaline because the enzyme that catalyses the formation of adrenaline from noradrenaline (phenylethanolamine-*N*-methyltransferase; PNMT) is activated by the high local concentration of steroids present in blood draining from cortex to medulla. Because PNMT is found in appreciable quantities only in the adrenal medulla and the brain, extra-adrenal catecholamine synthesis leads predominantly to noradrenaline (due to a lack of stimulation of PNMT). The findings in this series, however, demonstrated three adrenal phaeochromocytomas with excessive secretion of both adrenaline and noradrenaline, and eight showed an increased secretion of dopamine, demonstrating that in some tumours the metabolic pathway for catecholamine synthesis can generate abnormally high amounts of all types of catecholamine.

It remains unknown which type of granule is associated with dopamine secretion. The predominance of noradrenaline-like granules (63 per cent) in a tumour secreting 14 900 nmol per day of dopamine and 1570 nmol per day of adrenaline (patient no. 10) suggests that dopamine may be stored in noradrenaline-type granules. This was confirmed in a tumour showing secretion of both dopamine and noradrenaline (5520 and 12 880 nmol per day respectively) and in which 93 per cent of granules were of noradrenaline type (patient no. 1). In contrast, only 13 per cent of the granules identified on four random fields were of noradrenaline type in a tumour secreting excessive amounts of both dopamine and noradrenaline (4236 and 1693 nmol per day respectively) (patient no. 9).

Two non-functional phaeochromocytomas had large numbers of secretory granules. The lack of any clinical signs suggestive of excessive catecholamine secretion and the normal values on repeated biochemical testing suggests that these tumours did not secrete any of the stored catecholamines. No dramatic intraoperative changes in blood pressure occurred and, in the absence of intraoperative measurements of plasma catecholamine levels, it is impossible to know whether manipulation of these tumours induced release of stored catecholamines. The inability of these tumours to mobilize stored secretory granules may represent a deficit in one of the cytoplasmic proteins involved in the fusion of granules with the plasma membranes. An alternative explanation is that some of these secretory granules may be responsible for the secretion of some other hormone, not yet identified.

The lack of correlation between hormone output and granularity of tumour cells suggests that other factors determine the secretory patterns of phaeochromocytomas.

Acknowledgements

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Methods of repair and risk for reoperation in Swedish hernia surgery from 1992 to 1996

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Background Difficulties in obtaining and analysing outcome measures in hernia surgery may be an obstacle to necessary progress in non-specialized hospitals. Against this background a voluntary register was initiated in 1992 with the aim of describing and evaluating hernia surgery in participating units.

Methods Prospective registration of all hernia operations carried out in participating hospitals was undertaken using identification codes specific for each individual. Repair technique, complications, day surgery, type of anaesthesia, and reoperation for recurrence were recorded. Actuarial analysis was used to determine the cumulative incidence of reoperation. Relative risk for reoperation was estimated by the Cox proportional hazards model.

Results The number of participating hospitals and registered operations increased from eight and 1689 respectively in 1992 to 21 and 4056 in 1996. The use of mesh increased from 7 per cent of all operations in 1992 to 51 per cent in 1996. The proportion of operations done for recurrent hernia remained constant at 16–17 per cent throughout the 5-year study period. For all 12 542 herniorrhaphies registered, the cumulative incidence of reoperation at 2 years was 3 (95 per cent confidence interval 3–4) per cent. Postoperative complications, recurrent hernia, direct hernia and absorbable suture were associated with increased risk of reoperation for recurrence. An increased incidence of reoperation, although not statistically significant, was noted for conventional open repairs (Bassini, McVay, Marcy and others) *versus* the Shouldice technique.

Conclusion In this prospective audit an increasing use of mesh was observed for open and laparoscopic surgery, especially for bilateral and recurrent hernia operations. Reoperation rates decreased significantly between 1992 and 1995.

In evidence-based medicine the best external evidence is integrated with the expertise of the individual clinician[1]. To be aware of his or her proficiency and judgement, each surgeon should ideally have an easily available outcome measure, enabling comparisons to be made between outcomes from (randomized) controlled trials and the surgeon's own achievements.

Readily available outcome measurement in hernia surgery is of great importance because herniorrhaphy is a commonly performed procedure. In Sweden, with its 8·8 million inhabitants, there are 16 000–20 000 hernia operations per year, second only to cataract operation. Some 90 per cent of these operations are performed on patients above the age of 15 years. For hernia surgery the most important outcome from the patient's point of view is absence of recurrence[2].

In 1992 a hernia register was initiated in Sweden making it possible for one surgical unit to compare its data with aggregated figures for all participating hospitals. Using data from this register it is possible to describe changes in methods of repair and risk of reoperation for herniorrhaphies performed in Swedish hospitals. This forms the basis of the present report.

Patients and methods

The study comprises all patients older than 15 years who underwent hernia repair at units participating in the register between 1 January 1992 and 31 December 1996.

Hernia operations were documented according to a protocol with the following variables: time on waiting list, patient characteristics, type of hernia as defined during operation, method of repair, anaesthesia, postoperative complications within 1 month, and reoperation for recurrence. Follow-up examination was not mandatory. However, a 3-year follow-up was undertaken for all patients aged 15–80 years at operation who were operated on in 1992 at the eight hospitals that participated initially[3]. Patients with recurrence detected at this follow-up and who subsequently underwent reoperation were included in all calculations.

The register has been given permission to use identification codes specific for each citizen in Sweden[4]. This makes it possible to compare reoperation for recurrence with previous operations documented in the register. It also allows actuarial calculations and risk analyses to be adjusted for deaths of patients operated on.

Reoperation for recurrence was defined as any hernia operation, inguinal or femoral, in a groin previously operated on for hernia irrespective of type of hernia at the initial and subsequent procedure.

Surgical methods were classified as: (1) Shouldice technique; (2) conventional open repairs (Bassini, McVay, Marcy and other non-mesh methods with groin incision); (3) open mesh techniques with groin incision (Lichtenstein, Trabucco, plug methods); (4) open preperitoneal mesh insertion using midline (Stoppa) incision or transverse (Nyhus) incision; (5) laparoscopic transabdominal preperitoneal technique (TAPP); (6) laparoscopic total extraperitoneal technique (TEP).

Control and validation of data

To minimize input errors, data from operation protocols were fed into the computer twice. Routine control and correction of all data were performed at each centre, and numerous controls

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were carried out at the register centre before making final analyses.

External review of national quality register of hernia surgery

An external review of data from all operations performed at seven hospitals over a 2-month period (March and September 1995) was undertaken in 1996. The hospitals were selected taking into account geographical location and size in order to be representative of the 19 units participating in the register in 1995. The audit was undertaken by a senior Swedish surgeon who visited the seven hospitals. During visits he studied register outcome and validity (i.e. differences between data in the national quality register and hospital records) as well as organization, processing and consequences of quality register work.

Coverage. A total of 388 hernia operations had been registered at the seven units. It was possible to scrutinize the records of 385 cases (99 per cent). Six additional operations not recorded in the national quality register were identified in the hospital registers. Thus the quality register had a coverage of 388 (98 per cent) of 394 operations. Two of the six operations omitted had been documented in quality register protocols which, however, had not been fed into the computer. None of the patients undergoing these six operations had any divergent or complicated outcome.

Differences between quality register and hospital records. The following variables were investigated: emergency or elective operation, unilateral or bilateral operation, operating time, hospital stay, intraoperative complications, postoperative complications (30 days or less after operation), late complications (more than 30 days). The greatest difference between quality register data and hospital records was observed for operating time where a random difference of 5 min or more was observed for 42 operations (11 per cent). Fifteen postoperative complications were detected at the external review in addition to 51 complications already documented in the quality register. Of the 15 omitted postoperative complications, 11 consisted of haematoma or bleeding episodes. The overall value for the postoperative complication rate thereby increased from 13 to 17 per cent in the 385 operations covered by this external review.

Conclusion. Coverage of the national quality register is adequate (98 per cent) and no negative selection among omitted cases was observed. Greater emphasis on details of the quality register, notably postoperative complications, was considered essential.

Statistical analysis. Statistical analyses were performed with the Quest program[5], except for the Cox proportional hazards tests[6] for which the SPSS program (SPSS, Chicago, Illinois, USA) was used. The χ^2 test was used to determine differences between groups. Life-table analysis was used to measure cumulative incidence of reoperation for recurrence, considering operations performed since the start of the register. Unless otherwise stated, relative risk was estimated with the Cox proportional hazards model, first performing univariate analysis of assumed risk variables and then selecting variables with the highest 'univariate' relative risks for multivariate analysis. The proportional hazards assumption was examined as part of the Cox analyses. Interaction terms between risk factors were also introduced and examined in the multivariate analyses.

Results

From 1 January 1992 to 31 December 1996, 12 542 hernia repairs were performed on 11 378 patients, 10 438 men and 940 women. The mean(s.d.) ages of male and female patients were 60(16) and 60(19) years respectively. Of all herniorrhaphies, 2050 were recurrent hernia operations, 1679 of which were the consequence of previous procedures not recorded in the register, whereas 371 recurrences followed hernia repair performed within the frame of the register. *Table 1* shows, for each year, the number of participating hospitals, the total number of hernia repairs and the number of recurrent hernia operations. Eight hospitals participated in 1992 and 21 in 1996. The proportion of operations for recurrence remained constant at 16–17 per cent over the 5-year study period. The cumulative incidence of reoperation for recurrence following all 12 542 operations registered is illustrated in *Fig. 1*. At 2 years it was 3 (95 per cent confidence interval (c.i.) 3–4) per cent and at 3 years it was 4 (95 per cent c.i. 4–5) per cent.

Fig. 2 illustrates the risk of reoperation for recurrence following herniorrhaphies performed in 1992 and 1995 at the eight hospitals that participated initially. During these two periods 1689 and 1346 hernia repairs respectively were performed, 60 and 27 of which had been reoperated on by the end of 1993 and 1996 respectively. At 12 and 24 months the cumulative incidence was 2 (95 per cent c.i. 2–3) per cent and 4 (95 per cent c.i. 3–5) per cent for operations done in 1992 and 1 (95 per cent c.i. 1–2) per cent and 3 (95 per cent c.i. 1–4) per cent for those done in 1995. The relative risk for reoperation following a groin hernia repair in 1995 compared with 1992 was 0·55 (95 per cent c.i. 0·35–0·86) (log rank test). The use of absorbable sutures in these units fell from 87 per cent of all repairs to 27 per cent in 1995, a statistically significant difference (95 per cent c.i. 57–63 per cent).

Significant changes were also observed in the methods used for repair (*Table 2*). The use of conventional open repairs declined from 68 to 24 per cent, whereas the Shouldice technique, open mesh methods and laparoscopy were all used more frequently in 1995 than in 1992. The incidence of postoperative complications and the proportion of direct hernia in relation to all hernias did not differ significantly between 1992 and 1995.

Methods of repair used for all herniorrhaphies during the period studied are illustrated in *Fig. 3*. Operations with conventional open repair apart from the Shouldice technique fell from 68 per cent in 1992 to 18 per cent in 1996. The Shouldice technique was used in 26 per cent of

Table 1 National quality register of hernia surgery

	1992	1993	1994	1995	1996	Total
No. of hospitals	8	8	9	19	21	
No. of hernias	1689	1643	1834	3320	4056	12542
Recurrent hernia	278 (16)	259 (16)	311 (17)	564 (17)	638 (16)	2050 (16)
Recurrent hernia following previously registered operation	16	62	72	69	152	371

Values in parentheses are percentages

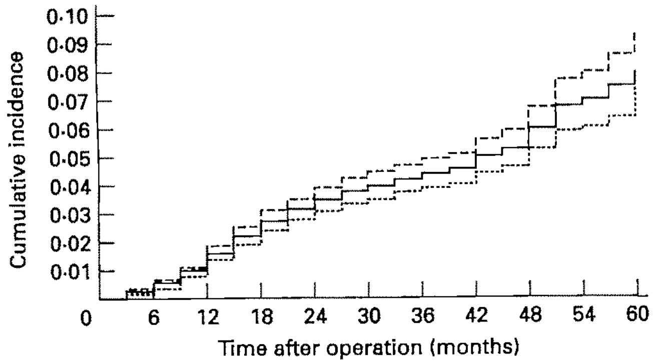

Fig. 1 Cumulative incidence of reoperation: ———, incidence; - - - - -, lower 95 per cent confidence interval (c.i.); – – –, upper 95 per cent c.i.

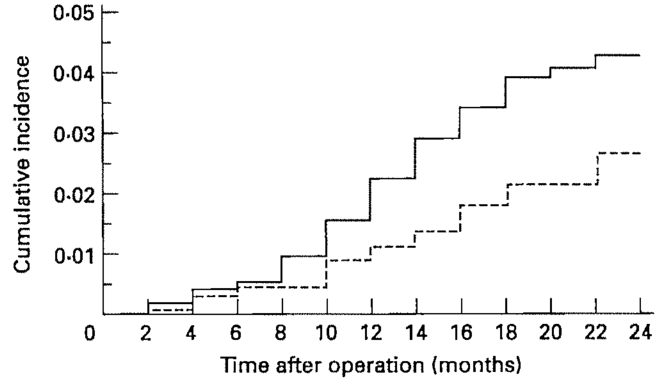

Fig. 2 Cumulative incidence of reoperation following herniorrhaphies performed in 1992 (———; 1689 operations) and 1995 (– – – –; 1346 operations) in eight hospitals. Actuarial analysis of reoperations from 1 January 1992 to 31 December 1993 and from 1 January 1995 to 31 December 1996 respectively

Table 2 Hernia repair methods used in the initial eight hospitals

	Percentage of repairs	
Method	1992 ($n = 1689$)	1995 ($n = 1346$)
Shouldice	26	42
'Other open'*	68	24
Mesh, groin incision†	1	12
Mesh, preperitoneal open, transverse or midline incision‡	<1	6
TAPP	4	11
TEP	0	5

*Bassini, McVay, Marcy and other open non-mesh methods; †Lichtenstein, Trabucco, plug methods; ‡Stoppa or Nyhus incision. TAPP, laparoscopic transabdominal preperitoneal technique; TEP, laparoscopic total extraperitoneal technique. $\chi^2 = 712$, 5 d.f., $P < 0{\cdot}001$

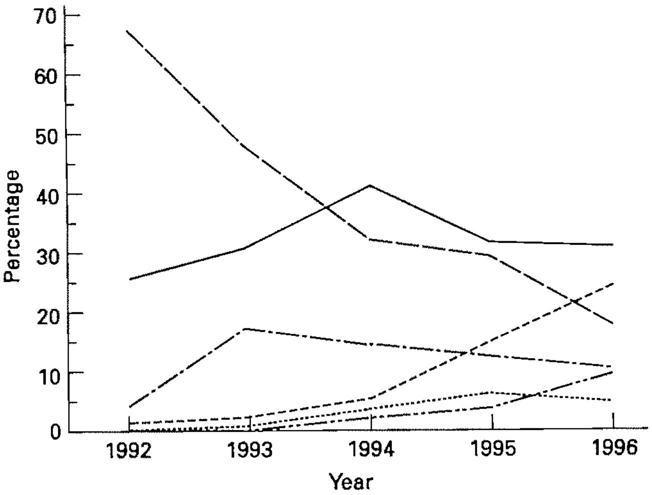

Fig. 3 Methods of hernia repair from 1992 to 1996: ———, Shouldice; ————, other open; – – –, mesh, groin incision; - - - - -, mesh, preperitoneal, transverse or midline incision; —·—·—, laparoscopic transabdominal preperitoneal technique; —··—··—, laparoscopic total extraperitoneal technique

all operations in 1992, in 41 per cent of all repairs in 1994 and in 31 per cent in 1996. The use of mesh increased from 7 per cent in 1992 to 51 per cent in 1996. Of all primary and recurrent hernia operations performed in 1996, 46 and 76 per cent respectively were done with a prosthesis. Very few meshes were applied via groin incisions before 1994 but the Lichtenstein and more recently the plug methods were used increasingly thereafter, and in 1996 25 per cent of all hernia repairs were performed using these techniques. TAPP and TEP techniques were used in 11 and 10 per cent respectively in 1996, whereas the preperitoneal open route for applying mesh was utilized in 6 per cent of all procedures that year. Some 820 operations were done bilaterally, 65 per cent of these laparoscopically, 9 per cent with preperitoneal mesh insertion according to Nyhus *et al.*[7] or Stoppa[8], and 6 per cent with mesh application via a groin incision. Overall, a mesh prosthesis was used in 81 per cent of bilateral operations, compared with 31 per cent of 11 722 unilateral procedures, a difference of 50 (95 per cent c.i. 47–53) per cent.

The use of day-case surgery increased from 557 (33 per cent) of 1689 operations in 1992 to 2102 (52 per cent) of 4056 operations performed in 1996. In 1996 general anaesthesia, regional (epidural, spinal) anaesthesia and local anaesthesia were used for 49, 49 and 2 per cent respectively of all operations.

Tables 3 and *4* illustrate the relative risks for reoperation for recurrence using data from all 12 542 operations and the subsequent 371 reoperations. Sex, hernia side (right *versus* left), size of the catchment area of the hospital (100 000 or more *versus* fewer than 100 000 inhabitants) and bilateral surgery were not associated with a relative risk significantly different from one in univariate analysis. These variables were therefore not considered in multivariate analysis. Age of patient (median or above *versus* younger), indication for surgery (emergency *versus* elective operation) and hospital stay (day-case surgery *versus* hospital stay) were tested in multivariate analysis and found not to be associated with enhanced risk of reoperation for recurrence. As shown in *Table 3*, a significantly increased relative risk was observed for postoperative complications within 30 days of surgery, for recurrent hernia, for direct hernia and for absorbable suture. There were no statistically significant differences between the surgical methods used (*Table 4*), although 'conventional open repairs' came very close to an increased risk.

An analysis of all 2050 recurrent hernia repairs is shown in *Table 5*. In this analysis it was considered essential to separate repairs with preperitoneal mesh insertion using midline or transverse incision from open mesh techniques with a groin incision. The former group was used as a reference. A tendency towards a lower risk for laparoscopic repairs was observed. However, no statistically significant difference between repair methods could be identified.

Table 3 Variables tested for relative risk for reoperation for recurrence following 12 542 hernia operations

Variable	No. of operations	No. of reoperations	Relative risk*
Postoperative complication†	1128	61	2·31 (1·75–3·04)
Operation for recurrence	2050	119	2·14 (1·69–2·71)
Direct hernia	5442	222	1·71 (1·38–2·11)
Absorbable suture	3131	188	1·60 (1·24–2·08)

Values in parentheses are 95 per cent confidence intervals. *Adjusted for age of patient, indication for surgery (acute or elective), method of repair, day-case surgery or hospital stay; †a postoperative complication within 30 days of surgery was noted for 9 per cent of all operations (haematoma 4 per cent, infection 1 per cent, neuralgia 1 per cent, recurrence <1 per cent, miscellaneous 2 per cent)

Table 4 Relative risk for reoperation for recurrence following 12 542 hernia operations emloying various techniques of repair

Method of repair	No. of operations	No. of reoperations	Relative risk*
Shouldice	4012	84	1·00 (reference)
Laparoscopy†	2048	39	1·03 (0·69–1·54)
Mesh open‡	2217	43	1·15 (0·77–1·72)
Other open§	4265	205	1·28 (0·98–1·69)

Values in parentheses are 95 per cent confidence intervals. *Adjusted for anatomy of hernia, primary or recurrent hernia, suture material, age of patient, postoperative complication (yes or no), day-case surgery or in-hospital treatment, and indication for surgery (acute or elective). †Transabdominal preperitoneal or total extraperitoneal technique. ‡All open and preperitoneal mesh techniques; §Bassini, McVay, Marcy and other open non-mesh repairs

Table 5 Relative risk* for reoperation for recurrence after various repairs of 2050 recurrent hernias

Method of repair	No. of operations	No. of reoperations	Relative risk
Mesh, preperitoneal open, transverse or midline incision†	316	8	1·00 (reference)
Laparoscopy‡	444	8	0·61 (0·23–1·63)
Shouldice	194	14	1·64 (0·66–4·06)
'Other open'§	681	69	1·71 (0·76–3·85)
Mesh, groin incision#	415	20	1·99 (0·87–4·53)

Values in parentheses are 95 per cent confidence intervals. *Adjusted for type of hernia, suture material and postoperative complications; †Stoppa or Nyhus incision; ‡transabdominal preperitoneal or total extraperitoneal technique; §Bassini, McVay, Marcy and other open non-mesh methods; #Lichtenstein, Trabucco, plug methods

Discussion

Results from the first 3 years of this audit have been published[9], demonstrating large variations in reoperation rates between participating units and the following risk factors for reoperation: postoperative complication, operation for recurrence, direct hernia and absorbable suture. The aim of the present report, covering 5 years and 12 542 hernia repairs, was to extend previous observations concerning risk factors for reoperation and to study time trends of repair methods and reoperation rates. The present study was an audit of effectiveness (i.e. results achieved in routine practice) as opposed to efficacy, achievements reached by experts under optimal conditions[10]. Evolution phases of new techniques as well as learning curves of surgeons were thus included in the study, which was based on prospectively collected data from a growing number of Swedish hospitals. It comprised approximately 15 per cent of hernia repairs performed in Sweden over the 5-year period. Internal validity of the data was checked and found to be adequate. External validity (how representative register data are of those from all Swedish units) cannot be estimated from register data alone. However, the register is open to all units and no selection criteria of any kind are used. In 1996 approximately 25 per cent of all herniorrhaphies performed in Sweden were recorded in the register.

The percentage of operations done for recurrent hernia remained constant (16–17 per cent) over the 5 years of this audit. In international[11–14] and Swedish[15–17] unselected case series, recurrent hernias have constituted 12–18 per cent of all hernias treated. As pointed out[12], this value is an indication of the quality of previous surgery. When a steady state has been reached it may also indicate the long-term reoperation rate within the population considered. However, the renewed interest in methodology of hernia repair, as witnessed by changes in methods of repair, indicates that hernia surgery (in Sweden) is far from reaching this steady state. According to actuarial analysis the cumulative incidence of reoperation was 4 per cent at 3 years. This may be considered an approximate index of the quality of recent hernia surgery. In a study[3] covering the eight hospitals initially participating in the present audit, it was observed that the recurrence rate at 3 years exceeded the reoperation rate by 39 per cent, using Marsden's definition of recurrence[18] (a weakness in the operating area necessitating a further operation or the provision of a truss). Thus, a recurrence rate of approximately 6 per cent at 3 years might be expected in the present audit. As this may represent only one-third of the recurrences at 25 years[19], the final recurrence rate may be expected to be about 18 per cent, which is in accordance with the finding that 16–17 per cent of herniorrhaphies in the present study were for recurrent hernia. It should be pointed out, however, that the relative risk for reoperation declined significantly between 1992 and 1995 in the eight hospitals that initially took part in the present audit. The drastic fall in use of absorbable sutures as well as changes in repair methods away from conventional open methods towards the Shouldice technique and to mesh techniques (open and laparoscopic) may to a large extent explain this improvement. However, an effect of register participation *per se* involving education and organization of hernia surgery cannot be excluded.

The changes observed in methods of repair indicate that a number of parallel learning curves were operating within Swedish hernia surgery during the time period studied. This is also underlined by the fact that the relative risk for reoperation using recently adopted methods (open mesh techniques and laparoscopy) was lower in this audit than in previous analyses[9,20]. The main time trend regarding methods of repair was the increasing use of mesh, whether performed by open techniques or laparoscopically. This was most pronounced in bilateral hernias, where mesh was used for 81 per cent of repairs. This may be one explanation why bilateral surgery did not appear as a risk factor for reoperation in this audit, in contrast to previous experience with the Shouldice technique[21,22]. Although the enhanced risk for reoperation observed for conventional open repairs *versus* the Shouldice technique was not statistically significant, it is nevertheless of interest as the former methods have been in use longer and Swedish surgeons should be more accustomed to them. The superiority of the Shouldice technique over other open methods for inguinal hernia repair is supported by a review of controlled trials[23]. As in our previous report[9], postoperative complications, operation for recurrence, direct hernia and absorbable sutures were associated with an increased risk for reoperation in the present extended analysis.

In centres with a special interest in open hernia surgery, local anaesthesia has been used extensively with excellent outcome[24–26]. In contrast, only 2 per cent of all herniorrhaphies registered in the present audit used this form of anaesthesia, which in Denmark has been found to save resources with high patient satisfaction and a low complication rate[27]. Further trials of anaesthesia for groin hernia would seem to be indicated in Sweden.

The present study has demonstrated an increasing use of mesh, most pronounced in operations for recurrent and bilateral hernias. With respect to avoidance of reoperation, it may be concluded that the Shouldice repair has not been superseded by mesh techniques. The audit confirms that day surgery is safe and that absorbable sutures should be avoided. A recent reduction in reoperation rate at the eight hospitals initially aligned to the hernia register seems to suggest that an improvement of Swedish hernia surgery has been initiated. Although a register of the present type may be used to define outcome differences between units[3,9], its main function is to demonstrate the effectiveness of surgical techniques in common use and to define variables associated with adverse outcome.

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Water-soluble contrast study predicts the need for early surgery in adhesive small bowel obstruction

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Background The optimal period of conservative treatment for adhesive small bowel obstruction remains controversial. This study sought to determine whether a 24-h abdominal radiograph after oral Urografin is a reliable indicator for operation in patients with adhesive small bowel obstruction.

Methods One hundred and sixty-one patients who suffered from adhesive intestinal obstruction without clinical evidence of strangulation or gangrene underwent a Urografin study. Some 40 ml Urografin mixed with 40 ml distilled water was administered either orally or via a nasogastric tube to each patient. Serial plain abdominal radiographs were taken 4, 8, 16 and 24 h later. If an earlier plain radiograph showed that contrast medium had reached the ascending colon, subsequent radiographs were not taken.

Results Contrast medium reached the colon within 24 h in 112 patients (70 per cent). These patients were all treated successfully with non-operative methods. Contrast medium was not observed in the colon within the first 24 h in 49 patients (30 per cent). Operation was performed in 47 of these patients and non-operative treatment was given in two. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of Urografin reaching the colon within 24 h as an indicator for non-operative treatment were 98, 100, 99, 100 and 96 per cent respectively.

Conclusion All patients with evidence of Urografin reaching the colon within 24 h were treated successfully with non-operative methods. The results of this prospective study suggest that patients with adhesive intestinal obstruction in whom contrast medium fails to reach the colon within 24 h should receive prompt surgical intervention.

Postoperative adhesion obstruction is thought to be the most common cause of small bowel obstruction in adults. Its management is still controversial[1–4]. It has been reported that early operation for any patient with complete intestinal obstruction prevents the risk of strangulation or bowel ischaemia[5–7]. Complete intestinal obstruction is usually defined as the complete lack of stool or flatus and absence of bowel gas distal to the site of obstruction on a plain abdominal radiograph; however, this definition is impractical[8,9]. Significant complications were reported in operations that were delayed for more than 48 h in patients with adhesion obstruction[10].

To prevent the development of strangulation or gangrene, early prediction of whether an episode of small bowel obstruction will resolve spontaneously is essential. In this prospective study, it was investigated whether contrast medium followed for 24 h can be a reliable indicator of the need for operation in small bowel obstruction.

Patients and methods

One hundred and eighty-eight patients with postoperative intestinal obstruction, who were admitted to the Department of Emergency Medicine between 1 August 1994 and 28 February 1997, were included in this prospective study. Intestinal obstruction was diagnosed on the clinical presentation of abdominal pain, distension, vomiting and abnormal bowel sounds, and was confirmed by the finding of dilated loops of small bowel and air fluid levels on plain abdominal radiography. Eleven patients with symptoms and signs of peritonitis within 24 h of admission, seven with peritonitis due to cancer, six aged less than 15 years and three patients whose intestinal obstruction occurred less than 30 days after an abdominal operation were excluded. A total of 161 patients completed this study, of whom 81 were women. The patients' age ranged from 20 to 84 (mean 57) years.

On admission, patients were evaluated by one of the surgical house staff. A detailed history was taken and after physical examination an erect plain abdominal radiograph was taken for each patient. If an intestinal obstruction was diagnosed, hydration with Ringer's lactate solution and gastric decompression with a nasogastric tube was initiated.

Some 40 ml Urografin (0·1 g sodium diatrizoate and 0·66 g meglumine diatrizoate per ml; Schering, Berlin, Germany) mixed with 40 ml distilled water was administered to each patient either orally or via a nasogastric tube. Serial plain abdominal radiographs were taken 4, 8, 16 and 24 h after Urografin ingestion. Subsequent plain abdominal radiography was cancelled if a previous plain radiograph showed the contrast medium reaching the ascending colon.

Patients in whom plain radiography demonstrated contrast medium in the ascending colon within 24 h after Urografin ingestion were placed on a test water or a liquid diet followed by a soft diet. Patients in whom Urografin failed to empty into the colon within 24 h either underwent operation or received non-operative treatment based on the presence or absence of clinical evidence of strangulation or gangrene, including fever, intractable pain, leucocytosis and peritonitis. The following data were collected for each patient: signs and symptoms, age, sex, type of previous operation, and outcome of treatment.

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Table 1 The clinical features of 161 patients who underwent a Urografin study

	No. of patients ($n = 161$)
Symptoms	
Abdominal pain	145(90)
Constipation	130(81)
Vomiting	60(37)
Previous surgery	
Upper abdomen	80(50)
Lower abdomen	81(50)

Values in parentheses are percentages

Results

The characteristics of the 161 patients who underwent Urografin study are shown in *Table 1*. Plain radiographs showed Urografin reaching the colon within 24 h in 112 patients (70 per cent). All of these patients were successfully treated with non-operative management. Of the 49 patients (30 per cent) in whom emptying of contrast medium into the colon was not found within 24 h, 47 underwent operation within 2–16 h of Urografin ingestion, and two were discharged after 5 and 6 days of conservative treatment. Of the 47 patients who received surgical treatment, 16 had peritonitis, 12 had intractable pain, 11 had leucocytosis and eight had fever. All of the surgically treated patients received enterolysis, of whom six required segmental bowel resection for bowel ischaemia. One patient developed pneumonia and one patient a wound infection. There was no postoperative death.

The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the finding of contrast medium reaching the colon within 24 h as an indicator for non-operative treatment were 98, 100, 99, 100 and 96 per cent respectively. A false-negative result was noted in two patients, a 24-year-old man who had underwent appendicectomy 4 months before the test and a 31-year-old woman who had a caesarean section 7 months before the test.

There was no evidence of complications associated with Urografin ingestion, such as hypovolaemic shock, fluid and electrolyte imbalance, allergy or aspiration pneumonia.

Discussion

Controversy still exists regarding the optimal period of conservative treatment before surgical intervention in patients with adhesive small bowel obstruction. Seror *et al.*[8] reported that non-operative management of up to 5 days' duration can be used safely for the majority of patients with postoperative small bowel obstruction. Hofstetter[11] suggested that small bowel obstruction should be treated surgically if obstruction is not resolved within 12 h of conservative treatment. Brolin and colleagues[9] found that failure of conservative treatment of small bowel obstruction requires prompt laparotomy, usually within 24 h. Sosa and Gardner[10] found that patients with adhesive small bowel obstruction may be treated non-operatively for 24–48 h, if no sign of strangulation is noted. Assalia *et al.*[12] recommended that operation should be considered for any patient with bowel obstruction which does not improve after 48 h of conservative treatment. Bizer *et al.*[13] suggested that 48–72 h is a sufficient period for non-operative management. The possibility of resolution of small bowel obstruction must be weighed against the need to decrease the complications of delayed surgery. The present results suggest that operation should be performed in patients in whom contrast medium fails to reach the colon within 24 h.

Various methods have been used to predict which patients will best benefit from non-operative treatment. Barium and water-soluble contrast medium have also been used to evaluate postoperative adhesion obstruction[5,11,14–22]. Some authors prefer barium to water-soluble contrast medium because it is not as easily diluted by enteric fluid, does not have a peristaltic effect on the bowel and enhances mucosal detail on radiography[5,15]. However, barium study may be dangerous in cases of nearly complete obstruction as it may become inspissated above the level of obstruction or barium may spread into the peritoneal cavity if perforation occurs or is present[16,23]. The present authors therefore recommend the use of water-soluble contrast medium because it is non-toxic if accidently spread into the peritoneal cavity. Furthermore, water-soluble contrast medium of high osmolarity can accelerate the resolution of postoperative ileus and enhance the resolution of adhesive bowel obstruction[11,18–20].

A prospective randomized trial by Assalia *et al.*[12] found that Gastrografin (Schering) has a therapeutic effect in adhesive small bowel obstruction and also aids in the early diagnosis of patients who require operation. However, a recent study found that water-soluble contrast medium has no therapeutic effect on postoperative small bowel obstruction[21]. The possible mechanism by which oral Gastrografin increases intestinal motility resulting in rapid passage of food contents through the bowel is that the high osmolarity of Gastrografin promotes proximal bowel distension and thus increases the gradient pressure across the obstructing area[22]. In addition to the dilution of bowel contents and the effects of a wetting agent, water-soluble contrast medium may allow easier passage of food contents through the narrowed lumen, and also decrease bowel wall oedema and enhance bowel peristalsis[19,20,22].

Urografin is a water-soluble contrast medium of high osmolarity which is used in intravenous and retrograde urography and angiography. It has been suggested that water-soluble contrast medium is contraindicated for the evaluation of suspected small bowel obstruction because of the possibility of shock induced by increased intraluminal volume. The high osmolarity of Urografin can draw significant amounts of fluid from both the intravascular space and extracellular space into the gastrointestinal lumen. However, the degree of fluid shift is dependent on the osmolarity and volume of the contrast medium. In this study only 40 ml Urografin was used, and no fluid and electrolyte imbalance or shock was found.

Spontaneous passage of stool was noted in 31 patients after Urografin ingestion. This suggests that Urografin may facilitate bowel movement as has been reported previously[18–20]. Oral intake can be initiated in patients for whom contrast medium reaches the colon within 24 h. Digestants and saline laxative are added to stimulate bowel movement. All of these patients started oral intake and the obstruction resolved 8–46 h after the Urografin study, including patients who experienced abdominal pain during oral intake. Therefore, abdominal pain is not a contraindication for oral intake in patients with partial bowel obstruction.

In conclusion, all of the patients with adhesive small bowel obstruction in whom contrast medium reached the colon within 24 h were successfully treated non-operatively and 96 per cent of patients who failed to show contrast medium emptying into the colon within 24 h were treated surgically. These results suggest that surgery should be performed in patients with adhesive small bowel obstruction when contrast medium fails to empty into the colon within 24 h.

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Advancement sleeve flaps for treatment of severe perianal Crohn's disease

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Background Traditionally proctectomy has been the treatment for severe, complex fistula *in ano* from Crohn's disease. However, based on the success of rectal advancement flaps in Crohn's disease, circumferential transanal sleeve advancement flaps (TSAFs) were proposed for this subgroup of patients with severe fistula.

Methods From 1991 to 1995, 13 patients (12 women) with severe perianal Crohn's disease and multiple fistula tracts underwent a TSAF procedure. Data were collected retrospectively using a standard data sheet.

Results There were no postoperative deaths or major morbidity. One year after surgery, the fistula had healed in eight of 13 patients (with three requiring additional surgery before healing). Of patients in whom the procedure failed, three underwent proctectomy for progression of disease and the other two had recurrence of a rectovaginal fistula 6 and 8 months after surgery. Of six variables evaluated (previous procedure, steroid use, steroid dosage, associated Crohn's disease, associated procedures and diverting stoma), only associated procedures were significantly related to a successful outcome ($P = 0{\cdot}008$).

Conclusion Some patients with severe perianal Crohn's fistula and a relatively normal rectum can be offered TSAFs. Even with successful outcome in eight of 13 patients, this may still be a viable option if the only alternative would be total proctocolectomy and a permanent stoma.

The management of perianal fistulas associated with Crohn's disease is often challenging and should be tailored to the specific patient. The surgical treatment of these perianal manifestations is based on the location and complexity of the fistula, the presence or absence of concomitant proctitis, sphincteric competence and the severity of accompanying anal canal disease[1].

Patients with symptomatic low-lying simple fistulas involving minimum sphincter musculature without concomitant proctitis can be treated appropriately by fistulotomy[2–4]. Where faecal continence could be compromised by partial sphincter division in patients with trans-sphincteric or anovaginal fistulas, advancement of partial-thickness flaps has been proposed as the treatment of choice in selected patients with a normal rectum[5,6]. However, extensive ulceration or stricturing of the anal canal and transitional zone is a contraindication for the endoanal sliding advancement flap technique.

Definitive treatment of severe perianal Crohn's disease, including complex fistula *in ano* and rectovaginal and rectourethral fistula, has traditionally been proctectomy[7–9]. The technique of rectal sleeve advancement was described by Berman[10] in a woman with combined rectovaginal and cryptogenetic fistulas involving more than one-third of the anal circumference. Since 1991 the authors have used a similar technique for selected complex perianal fistulas resulting from Crohn's disease.

The purpose of this study was to examine the outcome after a transanal sleeve advancement flap (TSAF) procedure in a subgroup of patients with severe and symptomatic perianal Crohn's disease. The primary endpoint was the success rate, which was defined as healing of the fistulas and ulcers 1 year following surgery.

Patients and methods

Between August 1991 and May 1995, 13 patients with severe complex perianal Crohn's disease were treated surgically by one surgeon (V.W.F.) by TSAFs. TSAF repair was proposed as an alternative to proctectomy in patients with perianal Crohn's disease associated with serious and disabling symptoms, such as drainage of malodorous secretions, perianal discomfort and pain, difficulty with hygiene, and dispareunia lasting at least 6 months. Patients were considered eligible for TSAFs if they had multiple fistulous tracts (including extension to the vagina and/or urethra) and histopathologically proven Crohn's cavitating ulcerations of the anal canal with or without anal canal stenosis. Preoperative proctoscopy was performed in all patients to evaluate the rectum. Patients were not candidates for TSAFs if they had moderate to severe proctitis, rectal stricture or active sepsis. However, the procedure was considered after adequate control of sepsis with abscess drainage with or without seton placement and with or without antibiotic therapy.

A retrospective review of the medical records was conducted using a standard data sheet. Follow-up information was obtained by office visits or by telephone contact. Data were collected for parameters that might influence the success rate: previous surgical treatment for perianal Crohn's disease; steroid use; steroid dosage; presence, activity and location of Crohn's disease proximal to the anorectum; surgical procedures performed to treat proximal concomitant Crohn's disease at the same setting as TSAFs; and use of a diverting stoma and outcome.

Follow-up for evaluation of the success rate was at least 12 months starting from the TSAF procedure or stoma closure (when protective ostomy was used). The outcome was considered successful when healing of the fistula or ulcer with symptom reduction was observed 1 year following surgery independently of the need for additional minor surgical procedures. The χ^2 test

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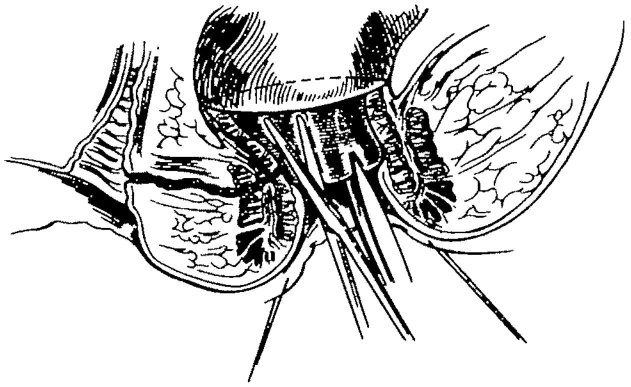

Fig. 1 A full-thickness sleeve flap is raised in a cephalad direction resulting in exposed denuded fibres of internal sphincter. Dissection is carried into the supralevator space until sufficient mobility is obtained

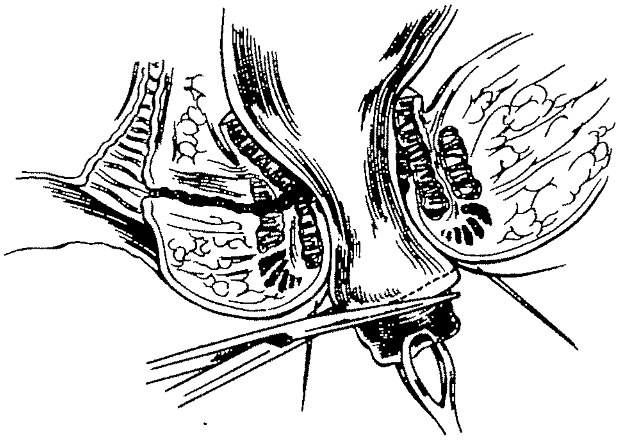

Fig. 2 After the internal opening of the fistula tract has been cored out and closed, the distal cylinder of diseased tissue is trimmed from the flap. The edge of the flap can then be sutured to the neodentate line

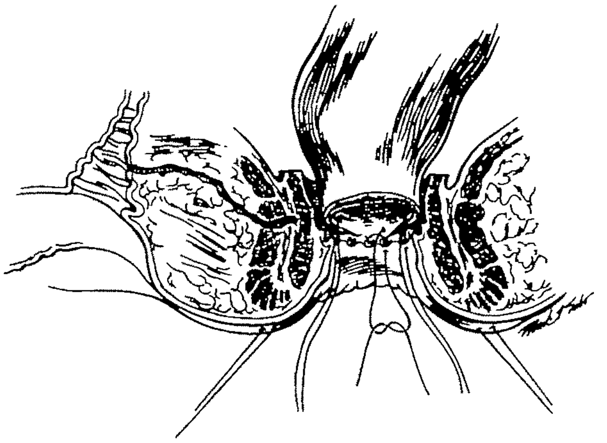

Fig. 3 The distal edge of the flap is sutured to the ridge of the new dentate line using interrupted 3/0 polyglactin sutures. A reinforcing layer of continuous 3/0 polyglactin suture is then added (not shown in this figure)

was used to evaluate the effect of a number of variables on the success rate.

Surgical technique

After full bowel preparation and induction of anaesthesia the patient is positioned in the prone jack-knife position. Polyglycolic acid sutures (no. 1) are applied at the anal verge as everting sutures to allow increased visualization of the anorectum. Adrenaline 1 : 200 000 is injected circumferentially into the anal canal and lower rectum. Using diathermy or scissors, a 90–100 per cent circumferential incision is made at or just below the dentate line, distal to the fistula opening or anal canal ulceration. A full-thickness (mucosa, submucosa and few fibres of internal sphincter) 'sleeve' flap is raised in a cephalad direction resulting in exposed denuded fibres of the internal sphincter. A few fibres of internal muscle are included in the sleeve of tissue owing to the inflammation from the fistula process. As much internal sphincter is preserved as possible. The dissection is carried into the supralevator space until sufficient mobility is achieved to permit the full thickness of rectum to be advanced caudally into the anal canal without tension (*Fig. 1*).

The fistula tracts are cored out and the anal opening is closed in layers with absorbable suture (2/0 polyglactin on a UR 6 needle) leaving the other side of the fistula open to allow drainage. The cylinder of distal diseased tissue is trimmed from the flap (*Fig. 2*). The flap is then supported with radially placed 2/0 polyglactin sutures from the undersurface of the flap to adjacent tissue (internal sphincter) to relieve tension and prevent retraction. The distal edge of the flap is sutured to the ridge of the new dentate line using interrupted 3/0 polyglactin sutures followed by a continuous reinforcing layer of 3/0 polyglactin sutures (*Fig. 3*).

In certain cases mobilization may be carried to the peritoneal reflection anteriorly to create more rectal wall mobility. Before operation the patient is warned about the possible need for diversion and for mobilization of the rectum via a transabdominal approach (so far the latter has not been necessary).

Results

There were 12 women and one man in the group. Median age at the time of surgery was 40 (range 25–60) years. All patients had complex severe perianal Crohn's disease including recurrent rectovaginal fistulas (four patients), associated rectovaginal and multiple perianal fistulas (seven patients) with anal stricture in two cases, associated rectourethral and perianal fistulas (one) and recurrent multiple anal canal ulceration (one). Symptoms related to perianal disease had been present for a median of 36 (range 10–180) months before operation. All patients but one had undergone previous surgery for perianal disease: transanal rectal advancement flap (five patients), debridement and draining seton placement (five) and fistulectomy (two).

At the time of the TSAF procedure ten patients were taking steroids (associated with azathioprine in two), one patient was taking 6-mercaptopurine and two patients were receiving no medication. Of the patients treated with steroids, four were receiving prednisone 10 mg daily and six 20 mg daily. The rectum was relatively spared in all patients; there were endoscopic signs of mucosal erythema in only three patients. Perianal disease was associated with proximal Crohn's disease in 12 patients (six with ileal and six with colonic disease). Six patients had a concomitant bowel resection (carried out at the same setting as the TSAF procedure): subtotal colectomy plus ileorectal anastomosis (one patient), ileotransverse resection and neoanastomosis (two), ileorectal resection

Table 1 Analysis of improvement (success rate)

Variable/Response	Improvement Total	Improvement No.	P*
Previous procedure			
Yes	12	7	0·41
No	1	1	
Drainage	8	5	0·65
Repair	4	2	
None	1	1	
Steroid use			
Yes	10	7	0·25
No	3	1	
Steroid dosage			
10	4	4	0·09
20	6	3	
Associated Crohn's disease			
Yes	12	8	0·19
No	1	0	
Small bowel	6	4	0·42
Colon	6	4	
None	1	0	
Associated procedures			
Yes	6	6	0·008†
No	7	2	
Diverting stoma			
Yes	8	6	0·21
No	5	2	

*χ^2 test; †significant ($P<0·05$)

and neoanastomosis (two), and right hemicolectomy with ileal stricturoplasty (one). All six patients who underwent a concomitant surgical procedure also had a covering stoma.

A TSAF procedure was performed with concomitant faecal diversion in eight patients. Five of these eight patients had the ostomy closed within a median of 5 (range 3–9) months. All five patients had a concomitant bowel resection. The sixth patient who had faecal diversion and a concomitant abdominal procedure for Crohn's disease at the time of the TSAF operation still had a protective stoma at the end of the study period because of faecal incontinence. This patient's continence failed to improve despite fistulectomy and sphincter repair performed 5 months after the TSAF procedure for recurrent fistulas. However, by the end of the study this patient did not show any fistula recurrence and no recurrences were observed during a total of 42 months after TSAF repair.

Two patients who had faecal diversion did not have a concomitant abdominal procedure. They underwent proctectomy for progressive perianal disease 5 and 15 months following a TSAF procedure.

There was no postoperative death or major morbidity. Median hospital stay for the whole group of patients was 7 (range 6–20) days. Median follow-up was 15 (range 12–48) months. Eight of the 13 patients had healing of the fistulas and ulcers 1 year following surgery with an overall success rate of 61 per cent. All patients with a successful outcome had a significant improvement in symptoms related to perianal disease; in particular, discharge of purulent secretions was resolved totally.

Of patients with a successful outcome three required additional surgery after the TSAF procedure: transanal rectal advancement flap for persistent sinus (two patients) and fistulectomy plus sphincter repair for recurrent fistulas associated with faecal incontinence (one). Of patients in whom the procedure failed, three underwent proctectomy because of recurrence and secondary progression of the perianal disease 5, 12 and 15 months following advancement flap surgery. The other two patients had recurrence of a rectovaginal fistula 6 and 8 months after surgery (the fistulas were still present at the last follow-up visit).

Success rate was then related to six primary variables of interest (*Table 1*). The success rate was significantly higher only for patients who underwent concomitant bowel resection (six of six *versus* two of seven; $P=0·008$). Although some of the results may appear to be clinically significant (absence of previous surgical perianal procedures and use of diverting stoma) they are not statistically significant because of the small sample size.

Discussion

Advancement flap repair of anal fistulas, with and without Crohn's disease, has been reported previously[5,6]. The flap technique has been demonstrated to be effective in the treatment of complex rectovaginal and perianal fistula because it incorporates a layer of intact healthy tissue into the high-pressure side of a high–low pressure shunt at the level of the anal canal[11]. The limitations of the 'conventional' flap include a variety of conditions found in perianal Crohn's disease such as extensive, circumferential ulceration and inflammation of the anal canal up to the anorectal ring. Such circumstances usually preclude any effective definitive treatment that leaves the patient with a functioning anal canal.

In recent years, encouraging results after local anorectal operations in patients with Crohn's disease have led surgeons to attempt more aggressive surgical management of Crohn's perianal disease[12,13]. As there is no cure for Crohn's disease an important goal of therapy should be symptom relief. The surgical strategy at this institution has therefore been to offer patients a chance of repair even in the presence of traditionally adverse features. TSAF repair has been offered as an alternative to proctectomy to patients with severely symptomatic perianal Crohn's disease that is causing overwhelming mental anguish.

The sleeve technique described here includes resection of a cylinder of diseased anal canal, with mobilization of the low rectum and advancement to the dentate line for a neodentate anastomosis. Such mobilization can usually be done with little or no tension, and also allows for apposition of two ends that contain little or no active inflammation.

Selection of patients is important to reduce the risk of a non-healing wound and worsening perianal disease. Acute perianal sepsis needs to be resolved before the flap procedure. The rectum should be relatively free from Crohn's disease at the time of surgery. However, the presence of an old erythema did not affect the final outcome in the present series. Treatment with steroids seems to be associated with better outcome, possibly because of remission of Crohn's disease elsewhere, as demonstrated in previous reports with flap procedures[6]. Patients needing a lower steroid dosage (10 mg) tended to have a higher success rate perhaps because of a potentially less aggressive inflammatory process. The importance of optimal control of proximal Crohn's disease for the success of this operation is implied from the successful outcome in all six patients who underwent proximal bowel resection in association with the advancement flap procedure (although one patient still had a stoma for faecal incontinence at the end of the study). Although use of a stoma is controversial, this observation supports the notion that proximal disease control will improve more distal disease[14,15].

A critical component of the selection process is the careful preoperative evaluation of local conditions. The examination includes precise anatomical definition and characterization of the fistulas, assessment of normal distensibility of the rectum, and demonstration of adequate mobility and pliability of the rectal wall by grasping the wall itself with a Babcock clamp. If necessary this examination should be performed under anaesthesia in the operating room.

Success after TSAF surgery is more likely when principles valid for the flap repair technique are adhered to closely[5]: careful haemostasis aided by adrenaline infiltration, adequate blood supply to the distal end of the 'sleeve' flap, avoidance of excessive tension on the invaginated rectum and complete debridement or excision of the fistula tract followed by layered closure of the internal opening. The role of faecal diversion is still controversial. Six of eight patients with a diverting stoma had a successful outcome compared with two of five patients treated without diversion. There were no set criteria for stoma construction in this series of patients. The use of a stoma depended on the surgeon's satisfaction with the technical conduct of the operation. However, considering the complexity of TSAFs, especially in inexperienced hands, use of stoma protection as a standard part of the procedure is recommended.

TSAFs allow additional perianal procedures to be performed. Two patients in this series required conventional rectal mucosal advancement flaps for a persistent sinus at the level of the anorectum. Another patient underwent fistulectomy and sphincter repair because of a persistent trans-sphincteric fistula associated with faecal incontinence. All three patients had a favourable outcome after these additional procedures, resulting in ultimate success following TSAF surgery.

The feasibility of conservative treatment of severe complex perianal Crohn's disease has been demonstrated. The TSAF procedure is associated with a relatively short hospital stay and an acceptable postoperative outcome. Although the study group was small and the follow-up period relatively short, the healing rate of 60 per cent is a quite impressive, especially in view of the significant reduction in symptoms.

In conclusion, TSAF can be offered as an effective surgical option in selected cases of severe Crohn's perianal disease associated with a normal rectum, especially if the only alternatives would be total proctocolectomy or permanent faecal diversion. The significant number (five of 13) of patients who failed to improve may be a reflection of the aggressiveness of the perianal disease. In this subgroup of patients radical treatment is always possible. Careful preoperative selection and meticulous surgical technique are required to achieve success.

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Pathophysiology and treatment of anterior rectal mucosal prolapse syndrome

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Background The study was designed to investigate the clinical presentation and laboratory findings of anterior rectal mucosal prolapse (ARMP) and to assess the results of two therapeutic modalities.

Methods Some 162 women with ARMP were assessed clinically and by defaecography and rectoanal manometry before and 1 year after one or two sessions of submucosal sclerotherapy or, in the case of recurrence, after transanal excision of the prolapsing mucosa.

Results Almost all patients reported a combination of symptoms suggesting obstructive defaecation. At defaecography anterior rectocele and excessive perineal descent at straining were present in 78 and 72 per cent respectively. The size of coexisting anterior rectocele and the extent of perineal descent were significantly related to the duration of the disease ($P < 0{\cdot}001$). One or, in the event of recurrence, two sessions of sclerotherapy led to an overall success rate of 51 per cent. Improvement after sclerotherapy was associated with partial recovery of anal tone and improvement of anal sampling and rectal sensation. Failure of sclerotherapy was related to rectocele of larger size ($P < 0{\cdot}001$) and a longer perineal descent at straining ($P < 0{\cdot}001$) than in patients with a successful outcome. Excision of the prolapsing mucosa resulted in symptomatic improvement in 42 of 47 patients and was associated with significant improvement of the defaecographic and manometric findings.

Conclusion ARMP is usually associated with anterior rectocele and excessive perineal descent. Submucosal sclerotherapy is successful in half of the cases, but only in the presence of a rather small anterior rectocele and short perineal descent. Failures after sclerotherapy can be treated by transanal excision of the prolapsing mucosa.

Obstructed defaecation is a common condition characterized by difficulty in completely emptying the rectum despite excessive straining at stool, sensation of a full rectum, a rather deep anal or rectal pain, and mucus and blood discharge from the rectum[1,2]. Several anatomical and functional disorders of the anorectum have been implicated as causative factors of the situation, including perineal descent[1,2], anterior rectal mucosal prolapse (ARMP)[1,3], anterior rectocele[4,5], inert and overt rectal prolapse[6], and paradoxical anal sphincter reaction at straining (anismus)[7]. It is not rare for more than one of the aforementioned disorders to coexist in the same patient who complains of symptoms suggesting obstructed defaecation[8] and, in this case, it is difficult to distinguish the causative disorder from what might be an epiphenomenon. Targeting the treatment to the correction of one individual disorder, wrongly considered as the predominant problem, and overlooking another may lead to failure to cure the patient's symptoms[9].

A variable incidence of anterior rectal mucosal prolapse in obstructed defaecation has been reported[1,2,8]. Sclerotherapy or excision of the prolapsing mucosa has been proposed for the treatment of the syndrome. The former technique is associated with a rather high recurrence rate of symptoms[3], while the latter seems to cure symptoms of obstructed defaecation in a high percentage of cases[5].

The aims of the present study were (1) to assess the pathophysiological features of ARMP syndrome in patients with obstructed defaecation; (2) to assess the efficacy of sclerotherapy; (3) to evaluate the efficacy of excisional therapy in those who do not respond to sclerotherapy; and (4) to investigate any alterations in the manometric and defaecographic findings after treatment.

Patients and methods

Between 1989 and 1996, 395 patients attended the outpatient clinics in two hospitals complaining of symptoms suggesting obstructive defaecation. Excluded were (1) those who had had any treatment in the anorectum and pelvis (sclerosing injections, haemorrhoidectomy, sphincterotomy, rectopexy, rectocele repair, hysterectomy, etc.); (2) 25 male patients with systemic illness possibly affecting anorectal function, such as diabetes mellitus, cerebrovascular stroke or Parkinson's disease; (3) patients with intussusception of the rectum, overt rectal prolapse and enterocele alone or in association with ARMP at defaecography; and (4) those with rectocele, solitary rectal ulcer and paradoxical sphincter reaction at stool without proctoscopic evidence of ARMP.

There were 162 women of mean(s.d.) age 51(14) years who participated in the study. These 162 patients had a sclerosing injection (1–2 ml 5 per cent phenol solution in arachis oil) into the prolapsing rectal mucosa through a proctoscope as the initial treatment. Patients who did not respond or had recurrent symptoms were given another session of sclerotherapy. Those who did not respond to reinjection underwent excision of the prolapsing mucosa, according to a technique similar to that described by Janssen and van Dijke[5]. All patients were called to attend a follow-up at 1 year after the final treatment. Assessment included symptomatic evaluation, manometry in all and defaecography in most patients. Forty-four women without

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Table 1 Incidence of presenting symptoms before treatment

Symptom	No. of patients ($n = 162$)
Straining during defaecation	127 (78)
Sense of incomplete evacuation	106 (65)
Rectal bleeding	84 (52)
Assisted evacuation (mediated digitally or by other object)	68 (42)
Sense of prolapse	62 (38)
Tenesmus or sense of foreign body in rectum	61 (38)
Perineal pain or discomfort	58 (36)
Interrupted defaecation	53 (33)
Mucus discharge	48 (30)
Pruritus ani	40 (25)
Abdominal or low back pain	31 (19)
Incontinence	26 (16)

Values in parentheses are percentages

Table 2 Defaecography variables in controls and in patients before therapy

Variable	Controls ($n = 44$)	Patients ($n = 162$)
Anterior rectocele*	10 (23)	126 (78)
Anterior rectal wall prolapse*	12 (27)	109 (67)
Paradoxical sphincter reaction*	0 (0)	8 (5)
Anorectal angle (°)†		
At rest	104(8)	121(16)
During squeezing	81(6)	83(9)
At straining	124(16)	144(21)
Perineal descent (cm)†		
At rest	2·2(0·7)	3·4(1·1)
During squeezing	0·9(0·7)	1·2(0·8)
At straining	5·6(1·3)	7·2(1·1)

*Values in parentheses are percentages; †values are mean(s.d.)

symptoms of obstructive defaecation and no evidence of ARMP, matched for age and parity with the women of the study, served as controls.

Symptoms were assessed according to a standard questionnaire (*Table 1*). Clinical assessment included inspection of the perineum at rest and at straining, and proctoscopy and sigmoidoscopy. Clinical outcome of any therapeutic procedure was graded as excellent (complete disappearance of symptoms), good (occasional symptoms, less than once every four defaecatory events), fair (constant symptoms of mild severity, or more than once every four defaecatory events) and poor (persistent symptoms). Excellent and good clinical results comprised a successful outcome, or clinical improvement. Clinical outcome refers to symptoms specifically related to the ARMP, these being the first seven listed in *Table 1*.

Stationary anorectal manometry was performed with an eight-lumen, water-perfused, polyvinyl catheter with an external diameter of 4·2 mm. A pressure transducer, incorporated in each perfusion line, was connected to a polygraph device (Synectics Medical, Stockholm, Sweden). The manometric tracings were shown on the screen of an on-line computer and were analysed using a dedicated software program. Calculation of the mean maximal resting and squeeze pressures, and the length of the sphincter and the high-pressure zone of the anus was performed according to standard definitions[10]. By inflating the endorectal balloon with air, the minimal volumes required to elicit transient and permanent call for stools, the maximal tolerable volume and rectal compliance were assessed. The parameters that characterize the rectoanal inhibitory reflex (RAIR) and the sampling events were also tested[10].

At evacuation proctography, the anorectal angle and its distance from the pubococcygeus line were measured at rest, during squeezing and during straining. The presence of any kind of anatomical abnormality such as rectocele or mucosal prolapse was also noted and measured[8,10,11].

Statistical analysis

Unless otherwise stated, numerical values are expressed as mean(s.d.). Statistical analysis was performed using Fisher's exact test, the Mann–Whitney *U* test and the Wilcoxon test for paired and unpaired values, and simple regression analysis, as appropriate. $P < 0·05$ was considered to be statistically significant.

Results

All but 17 women had a history of two or more vaginal deliveries. Presenting symptoms and clinical findings are shown in *Table 1*. Excessive straining during defaecation and a feeling of incomplete evacuation were the most common symptoms, followed by rectal bleeding. At proctoscopy, ARMP was detected in all patients. A solitary ulcer on the protruding mucosa was evident in 27 patients (17 per cent).

Table 3 Manometric variables of the controls and patients before therapeutic intervention

Variable	Controls ($n = 44$)	Patients ($n = 162$)
MMRP (cmH$_2$O)	64(12)	58(11)
MMSP (cmH$_2$O)	126(20)	98(26)
Total sphincter length (cm)	3·1(0·3)	2·0(0·4)
High-pressure zone (cm)	1·7(0·2)	1·2(0·3)
Sampling events		
Presence (no. of subjects)	39 of 44	103 of 162
Frequency (events per h)	8·0(1·6)	5·0(1·1)
Reduction of resting pressure (%)	59(14)	63(12)

Values are mean(s.d.). MMRP, mean maximal resting pressure; MMSP, mean maximal squeeze pressure

All patients exhibited some sort of abnormality at defaecography. The most common finding was an anterior rectocele larger than 2 cm, which was present in 78 per cent of the patients. Excessive perineal descent at rest and during straining was demonstrated in 72 per cent, while prolapse of the anterior rectal wall was evident in 67 per cent. A significant correlation was found between the duration of symptoms and the length of both the rectocele ($r = 0·76$, $P < 0·001$) and the perineal descent at straining ($r = 0·54$, $P < 0·001$). Similar abnormalities in the control group were significantly less common and less severe (*Table 2*).

Squeeze anal pressure ($P < 0·01$), total length of sphincter ($P < 0·001$) and high-pressure zone length ($P < 0·01$) were significantly lower in patients than in controls. In addition, sampling events were less commonly observed ($P < 0·05$) and with a lower frequency ($P < 0·001$) in patients than in controls (*Table 3*). During testing of the RAIR, the minimal rectal volume required to induce sustained relaxation of the internal anal sphincter was significantly lower in patients than in controls ($P < 0·01$). Furthermore, the rectal volumes required to induce transient or sustained desire to defaecate were significantly less in patients than in controls ($P < 0·05$) (*Table 4*).

Table 4 Rectoanal inhibitory reflex, rectal sensation and rectal compliance in controls and patients

Variable	Controls ($n = 44$)	Patients ($n = 162$)
Rectoanal inhibitory reflex		
Minimal rectal volume for transient IAS relaxation (ml)	28(5)	22(6)
Minimal rectal volume for sustained IAS relaxation (ml)	105(12)	81(21)
IAS residual pressure at 100 ml of rectal air (%)	46(4)	62(11)
Minimal rectal volume for transient desire to defaecate (ml)	90(13)	66(22)
Minimal rectal volume for sustained desire to defaecate (ml)	140(35)	102(18)
Maximal tolerable rectal volume (ml)	262(55)	289(37)
Rectal compliance (ml/cmH$_2$O)	10·9(2·0)	9·9(2·2)

Values are mean(s.d.). IAS, internal anal sphincter

Clinical outcome

One session of sclerotherapy led to clinical improvement in 30 per cent of the patients. Repeat sclerotherapy resulted in a satisfactory outcome in 26 per cent of the cases (*Fig. 1*). The severity and incidence of incontinence were not affected by sclerotherapy. The presence of perineal pain at the initial evaluation was significantly associated with a bad result following either one or two injection sessions ($P < 0\cdot01$).

Fourteen of the 44 patients with symptomatic improvement after one session of injection continued to exhibit ARMP at proctoscopy. No solitary rectal ulcer was evident (present in six of the 44 patients before sclerotherapy). Similarly, ARMP persisted at proctoscopy in 60 per cent of the patients with no symptomatic improvement. Solitary rectal ulcer persisted in 17 cases (present in 19 of the 105 cases before sclerotherapy). Similar results were obtained at proctoscopy, following the second session of injection.

Surgical excision of the prolapsing rectal mucosa resulted in symptomatic relief in 42 of 47 patients (*Fig. 1*). Incontinence was cured in only two of 11 patients. All five patients in whom surgical excision failed reported perineal pain as the main complaint at the initial presentation. At postoperative proctoscopy ARMP was evident in only one patient, while no solitary rectal ulcer was found (present in seven patients before surgery).

Laboratory findings after treatment

A successful outcome of one session of injection was associated with a significant decrease in the incidence of ARMP at defaecography (to one of 37), a significant increase in the resting anal pressure (71(6) cmH$_2$O; $P < 0\cdot01$) total sphincter length (3·3(0·2) cm; $P < 0\cdot05$) and frequency of sampling (8·9(0·9) events per h; $P < 0\cdot01$), and a significant decrease in rectal compliance (9·1(1·2) ml/cmH$_2$O; $P < 0\cdot01$). The defaecographic and manometric results were similar in patients with a successful outcome after reinjection. The presence of a large anterior rectocele was associated with a poor result after either one or two sessions of injection (rectocele size: successful outcome 2·4(0·3) cm *versus* failure 3·5(0·5) cm; $P < 0\cdot001$). Similarly, the extent of perineal descent adversely affected the outcome of the sclerosing injection (perineal descent at straining: successful outcome 6·4(0·7) cm *versus* failure 7·5(0·9) cm; $P < 0\cdot001$).

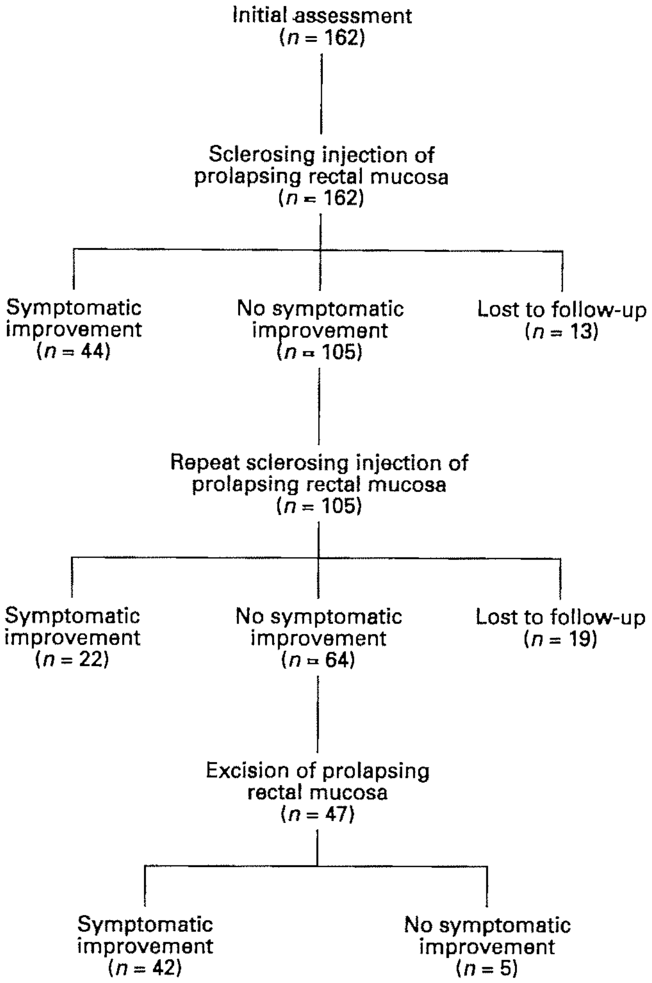

Fig. 1 Clinical outcome after the various procedures

Successful excision of the anterior mucosa was associated with (1) a significant reduction in the incidence of both the mucosal prolapse (one of 41) and the anterior rectocele (six of 41) ($P < 0\cdot001$); (2) a significant increase in mean maximal resting pressure (67(10) cmH$_2$O; $P < 0\cdot001$) and total sphincter length (2·6(0·4) cm; $P < 0\cdot01$); (3) a significant increase in the incidence (23 of 42; $P < 0\cdot05$) and frequency (8·1(1·1) events per h; $P < 0\cdot001$) of sampling events; and (4) a significant reduction in minimal rectal volumes inducing transient (47(12) ml) or sustained (67(11) ml) desire to defaecate ($P < 0\cdot01$) and in rectal compliance (6·8(1·7) ml/cmH$_2$O; $P < 0\cdot001$). Similar changes were seen in those in whom the procedure failed.

Discussion

In the majority of cases in the present series, ARMP presented clinically with obstructed defaecation. This is in accordance with some reports[1,5,12], but not with others[13]. Allen-Mersh *et al.*[3] observed a low incidence of symptoms of obstructed defaecation. Conversely, the incidence of incontinence in the present series was 16 per cent, much lower than the 40 per cent reported by Janssen and van Dijke[5], and higher than the 2 per cent reported by Allen-Mersh *et al.*[3]. These discrepancies in the clinical presentation of the condition could be attributed to differences in several parameters observed at first attendance, such as length of history, sex distribution, parity, severity of concomitant disorders or presence of systematic illness.

Defaecography demonstrated the presence of ARMP in two-thirds of the patients in whom the disorder was discovered at proctoscopy. Anterior rectocele was found to coexist in 78 per cent of cases, an incidence similar to that reported by Janssen and van Dijke[5]. The incidence of 72 per cent for perineal descent at straining in the present series is much higher than the value of 14 per cent reported by Allen-Mersh *et al.*[3]. This difference could be the result of the disorder being diagnosed by clinical inspection in their study and by defaecography in the present one. The long history of straining at stool and the fact that both the size of rectocele and perineal descent parallel the length of history in patients with obstructive defaecation and ARMP support the view that these disorders could be considered as precursors of complete rectal prolapse[1,13].

Patients with ARMP showed reduced anal pressures and impaired anal sampling function compared with normal individuals. This could be the result of the perineal descent that accompanies ARMP and is associated with pudendal neuropathy[14]. Other factors could also be implicated to explain reduced anal pressures, such as inhibition of the internal anal sphincter by the prolapsing mucosa by the activation of the RAIR, in a manner similar to that proposed for rectal intussusception[15,16], or by the triggering of rectal pressure waves, similar to those observed in rectal prolapse[17]. The improvement of anal sphincter pressures after successful treatment of ARMP, according to the present findings, supports the latter explanation.

The rectum of patients with ARMP appears to be more sensitive and less compliant than that in controls, possibly as a result of the mechanical inflammation and ischaemia of the prolapsing rectal mucosa, even in the absence of a solitary rectal ulcer, which was observed in 17 per cent of the patients in the present series. Besides, the histopathological changes of ARMP are similar to those of solitary rectal ulcer[13].

Conservative treatment of ARMP includes glycerine suppositories[3], submucosal phenol injections[3] and rubber band ligation[3,12]. Surgical treatment requires transanal excision[5]. Allen-Mersh *et al.*[3] reported that the three conservative approaches are equally effective, offering a permanent satisfactory result in approximately 43 per cent of patients, and a recurrence rate of 26 per cent over 10 years of follow-up, while 31 per cent of cases show no improvement at all. In the present series, symptomatic improvement after one or two sessions of sclerosing injection was reported by 66 patients (51 per cent). A satisfactory result after sclerotherapy was associated with improvement of anal sphincter function and rectal sensation. The presence of perineal pain as the main complaint before treatment, a large rectocele and excessive perineal descent were associated with unsatisfactory results after sclerotherapy.

Transanal excision of prolapsing anterior rectal mucosa offers a 90 per cent rate of symptomatic cure, mostly attributed to the reduction in size of the anterior rectocele. The postoperative increase in anal sphincter pressure, possibly as a result of the removal of inhibition of anal tone, prevents incontinence, despite the reduction in rectal compliance and perceived rectal volumes. Failure of the procedure to cure symptoms, despite the correction of ARMP and rectocele, was again associated with the presence of perineal pain as the main preoperative symptom. Advanced neuropathy of the pelvic musculature or coexisting slow transit constipation that has been overlooked may also contribute to failure.

In conclusion, sclerotherapy of the ARMP is successful only in the presence of a small anterior rectocele and short perineal descent. Transanal excision of the prolapsing anterior rectal mucosa offers high rates of symptomatic cure and improvement of anorectal function.

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Effect of a novel prosthetic anal neosphincter on human colonic blood flow

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Background An artificial anal sphincter has been developed which aimed to simulate the normal physiology of the anorectum. As a prelude to human implantation the present study reports the effect of inflation of this device on colonic perfusion in patients undergoing colectomy, which was assessed by using a laser Doppler scanner.

Methods Eleven patients (median age 49·8 (range 24·3–78·7) years) were studied. Five patients had inflammatory bowel disease (IBD). The neosphincter was placed around the bowel and progressively inflated. The model was designed so that blood flow changes to the colon under the neosphincter would be reflected in the distal segment of the bowel, which could be scanned by the laser Doppler scanner.

Results The blood flow in the colon distal to the device was significantly higher in patients with IBD (mean(s.e.m.) 288·6(71·9) *versus* 211·1(57·6) perfusion units; $P < 0·001$). The mean(s.e.m.) 'biological zero' value was 46(14) perfusion units. Blood flow distal to the neosphincter decreased progressively with increased sphincteric compression by 0·66 per cent per mmHg applied pressure in controls and 0·35 per cent per mmHg in patients with IBD ($P < 0·05$).

Conclusion These results suggest that at the planned operating occlusion pressure (less than 45 mmHg) this neosphincter should not put the vascularity of the human colon at risk.

Attempts have been made to develop a prosthetic anal sphincter as a solution for faecal incontinence but to date these devices have been associated with many complications and have not gained acceptance[1–4]. In contrast, urinary incontinence has been successfully treated using an inflatable circular cuff, the AMS 800, implanted around the urethra[5–8]. When inflated, this cuff produces a triangular shaped lumen, applying squeeze pressure to the urethra which exceeds intravesical pressure. A larger version of the same circular cuff prosthesis has been used to treat faecal incontinence in animals[9,10] and humans[3] but in early reports produced intestinal ischaemia at operating pressures which maintain continence[9,10]. This probably occurred because bowel is less tolerant to ischaemia than the urethra and also because the heterogeneous application of pressure by the above device has the potential to create localized high-pressure zones which may damage the bowel if it crenates into these areas[7].

An artificial anal sphincter has been developed[11] which aimed to overcome the risk of ischaemic complications by simulating the normal physiology of the anorectum (i.e. to flatten and angulate the bowel) and which did not produce ischaemic injury in an animal model[12]. In brief, the device consists of the sphincter element which is placed around the bowel just distal to the level of the pelvic diaphragm (approached via a laparotomy), a constant pressure balloon reservoir (with a sigmoid pressure–volume relationship) and a control pump. The sphincter component in turn comprises an inflatable linear expander which flattens the bowel against a gel-filled pillow while the balloon provides the hydraulic pressure source to drive the system. In this respect the operation of the pump and balloon are similar to that previously described in the AMS 800 unit.

The design is based on present understanding of the dynamics of flow for solid/semisolid materials which indicates that in order to retain a solid within a tube it may not be necessary to seal the end if an angle or 'kink' is incorporated in the tube[13,14]. In an *in vitro* study the inclusion of a 90° angle reduced the 'occlusion pressure' required to achieve continence for solids[15].

As a prelude to human implantation, the present study reports the effect of inflation of this prosthetic sphincter on the vascular perfusion of the human colon at various operating pressures. Blood flow measurement in the bowel wall using a prototype laser Doppler scanner[16] has already been described[17]. Laser Doppler imaging may give a composite value of the mural blood supply[18,19]. Since the prosthetic sphincter is opaque to laser light it was necessary to develop a model to permit measurement of blood flow changes in the colon in response to sphincteric compression.

Patients and methods

Eleven patients (seven men; median age 49·8 (range 24·3–78·7) years) were studied. Five patients underwent colectomy for inflammatory bowel disease (IBD) and six underwent colectomy for non-inflammatory conditions (rectal prolapse, one; carcinoma, five). In one patient with carcinoma, the right colon was supplied only by the ileocaecal artery because of previous surgery and was ischaemic. Bowel preparation with Picolax (Ferring Pharmaceuticals, Feltham, UK) and Klean-prep (Norgine, Harefield, UK) solution was instigated before operation. Routine biochemical and haematological investigations were carried out before and after surgery. Informed consent was obtained from all of the patients and the study was approved by the local ethics committee.

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Anaesthesia was induced with thiopentone and maintained with a nitrous oxide/oxygen/isoflurane mixture; all routine cardiorespiratory parameters were monitored continuously. A segment of colon approximately 25 cm long was prepared for the experiments as reported previously[17] so that all blood supply came from a proximal feeding vessel (end artery). The neosphincter was then placed around the bowel so that it encircled the whole circumference of the bowel including the end artery (*Fig. 1*). Upon inflation of the neosphincter, the blood supply to the colon under the expander would decrease and this decrease would be reflected in the blood flow in the distal segment of the bowel on scanning.

The separation between the expander and pillow was set to 22·5 mm and the expander was variably inflated to achieve inflation pressures of 30, 60 and 90 mmHg. The pressure applied by the sphincter on the bowel was measured three times at each stage by the station pullthrough technique using a Gaeltec CTU1 catheter tipped microtransducer (Gaeltec, Isle of Skye, UK).

The surface of the bowel was scanned using a laser Doppler scanner with the sphincter uninflated, at each pressure setting and with the mesentery clamped in order to establish a biological zero flow reading which was used as baseline[20]. Image processing software[16] was used to analyse blood flow to the colon proximal and distal to the sphincter on each scan and expressed in perfusion units. The unpaired *t* test was used to compare data.

Results

Anaesthetic parameters remained stable throughout the operations. There was no significant difference in pre- and postoperative haematological parameters.

A specimen series of scans during progressive inflation of the neosphincter is shown in *Fig. 2*. The operating occlusion pressures applied on to the bowel wall by the sphincter ($P_{Pullthrough}$) were approximately 0, 20, 38 and

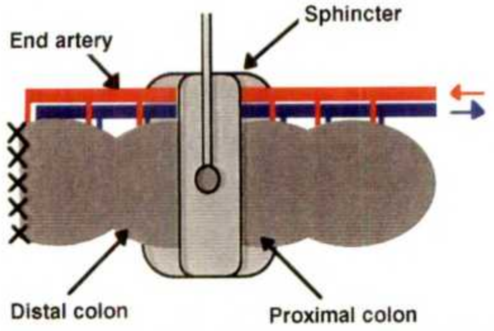


Fig. 1 Experimental arrangement for studying the blood supply distribution in the colon. The distal colon receives its blood supply from the end artery which passes under the neosphincter. Blood flow changes under the device should be reflected in the distal segment of the colon which can be scanned

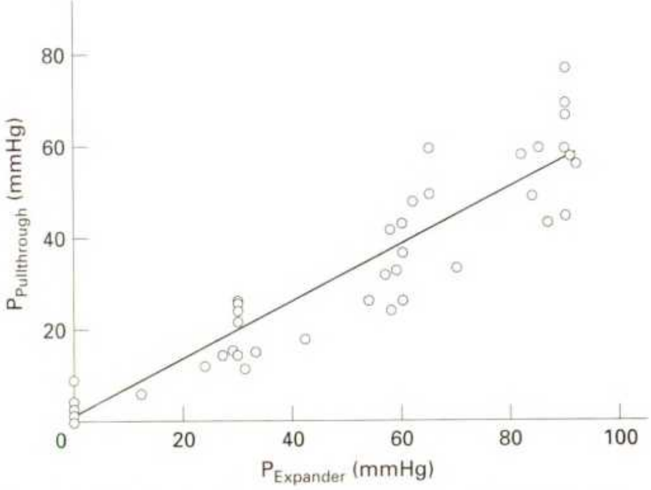
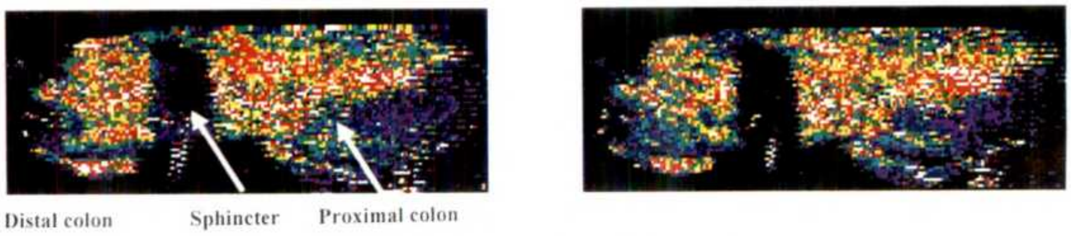
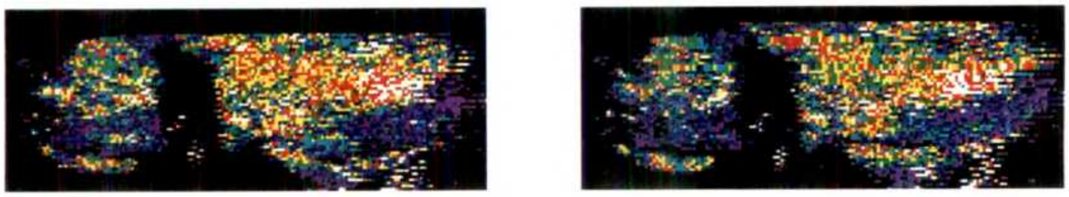


Fig. 3 Correlation of operating occlusion pressure on the bowel ($P_{Pullthrough}$) *versus* expander inflation pressure ($P_{Expander}$) for the 11 patients. Slope = 0·63, $r^2 = 0·88$



a $P_{expander} = 0$ mmHg

b $P_{expander} = 30$ mmHg



c $P_{expander} = 60$ mmHg

d $P_{expander} = 90$ mmHg

Fig. 2 Blood flow scans with progressive inflation of the neosphincter at expander inflation pressures of **a** 0 mmHg, **b** 30 mmHg, **c** 60 mmHg and **d** 90 mmHg

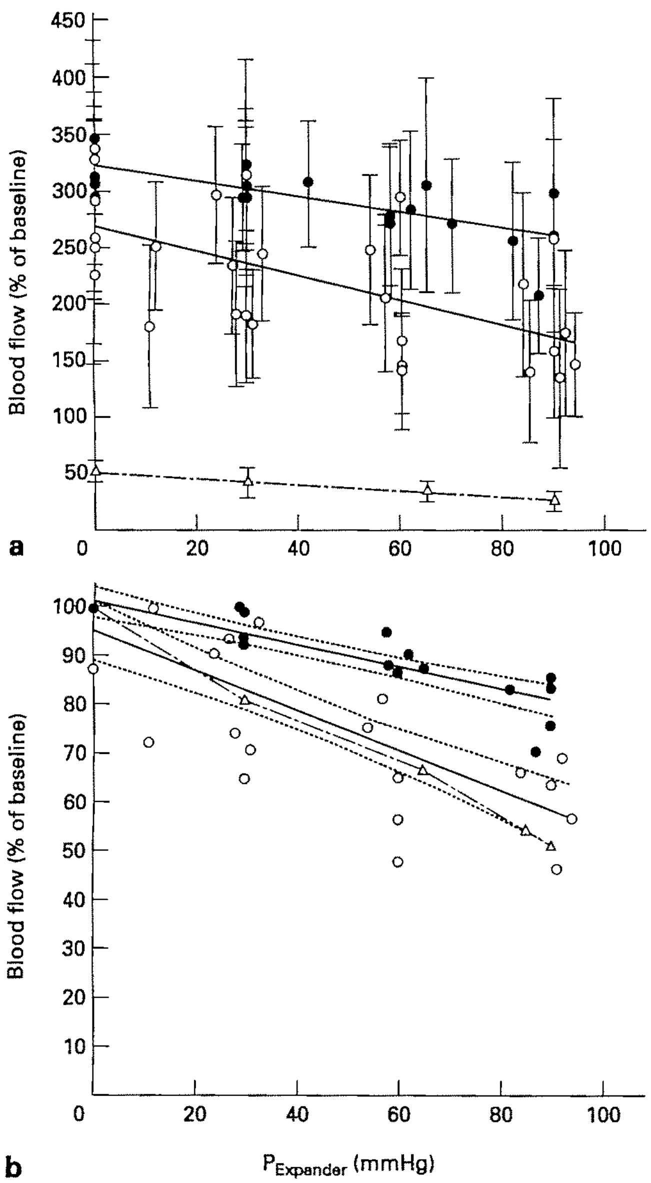


Fig. 4 Blood flow in the colon distal to the neosphincter *versus* progressive compression (P_{Expander}) in patients with inflammatory (closed symbols) and non-inflammatory (open symbols) bowel disease expressed as mean(s.e.m.) perfusion units (a) and percentage of baseline values with 95 per cent confidence intervals (·····) (b). Data from the patient in whom the ileocaecal artery supplied the colon are also shown (Δ—·—·—Δ). Once the blood flow is normalized to percentage of baseline (b), the results for the latter patient lie within the 95 per cent confidence interval of the rest of the group. Some patients had more than one reading at each pressure level. Solid lines represent estimated regression lines

58 mmHg respectively as the transmission factor was approximately 0·63 mmHg occlusion pressure per mmHg expander pressure (*Fig. 3*). This produced a progressive reduction of blood flow to 64, 54 and 48 per cent of baseline levels respectively, taking into account biological zero value.

There was a small but significant decrease in blood flow in the colon proximal to the neosphincter with progressive inflation of the device (13 per cent, $P<0·001$) when data for all the patients were pooled together, but no difference in individual patients. The blood flow in the colon distal to the device was significantly lower in the control group than that in patients with IBD (distal segment: mean(s.e.m.) 211·1(57·6) *versus* 288·6(71·9) perfusion units; $P<0·001$). The mean(s.e.m.) 'biological zero' value (i.e. the Doppler flow reading with all blood supply clamped) was 46(14) perfusion units and there was no significant difference between the two groups of patients ($P=0·88$).

Blood flow distal to the neosphincter decreased progressively with increased sphincteric compression (*Fig. 4*); this decrease amounted to 0·66 per cent per mmHg applied pressure in controls and 0·35 per cent per mmHg in patients with IBD ($P<0·05$).

Discussion

The development of a successful prosthetic anal sphincter would represent a major advance in the treatment of faecal incontinence. Use of circumferential occlusive devices has been limited predominantly by the development of intestinal ischaemia and ulceration in animal models[9,10,21] and in humans[22–25]. When used in animals for prolonged periods without pressure control, unacceptable complications occur[10,21]. When pressure was maintained below 50 mmHg no ischaemic injury ensued[9], which suggests that occlusive devices may be made to work if the pressure is kept low.

In an attempt to overcome ischaemic complications a prosthetic anal sphincter was designed which operates at occlusion pressures of only 40 mmHg[11,12,26]. This is achieved by incorporating angulation, which may enhance continence of solids at low occlusion pressures[15]. Since the device flattens the bowel and uses the 'hammock effect' to distribute pressure evenly, localized high-pressure points are prevented[26].

Before embarking on human implantation studies it was necessary to demonstrate that there was no critical reduction in blood flow to the gastrointestinal tract even at these relatively low occlusion pressures. To this end, a prototype laser Doppler scanner[16] was used. The depth of laser light penetration is approximately 6 mm in human colon[18]. Measurements therefore may represent a composite of transmural blood supply[18,19]. Differential measurement and correlation of mucosal and serosal blood flow using static laser probes was found to be unreliable[27], possibly because of transducer pressure and movement artefacts.

Since the neosphincter is opaque to laser light a model was developed to study the effect of the neosphincter on blood flow to bowel supplied by an end artery distal to the device. It is accepted, however, that this model suffers from two limitations: it cannot measure blood flow directly under the device and the operative preparation of the bowel for these experiments will inevitably result in a reduction of the baseline blood flow. The mesenteric vasculature, however, would not be ligated during the dissection in long-term implantation in patients and so both proximal and distal blood supply to the colon would be preserved. This would greatly increase the baseline blood flow.

The absolute baseline value of blood flow may not be as important for the analysis of the response to progressive compression (*Fig. 4*). Although patients with IBD are not suitable for such an artificial sphincter, their inclusion in this study serves to strengthen the hypothesis that irrespective of the baseline blood flow value differences in the response to pressure application can still be observed; in patients with IBD the bowel was less sensitive to the application of pressure. This may be related to the inflammatory infiltrate and fibrosis surrounding blood vessels making them less vulnerable to occlusion pressure.

Inflation of the neosphincter to occlusion pressures of 30, 60 and 90 mmHg produced a progressive decrease in blood flow to 64, 54 and 48 per cent of baseline level respectively. Although colorectal carcinoma promotes angiogenesis, this is generally a local tumour effect. Since all measurements were made at least 20 cm proximal to the neoplasm, it is unlikely that the colon in the control population was abnormal. Healthy intestine can tolerate a chronic reduction in blood supply to 50 per cent of baseline without irreversible changes[28,29], while colonic anastomoses have been shown to heal with blood flows as low as 30 per cent of baseline[30]. Although different methods were used to study intestinal blood supply in the above studies, the results of the present study suggest that at the planned sphincter operating pressure there should be no risk of ischaemic injury to the human colon. It is of note that the same operating pressures produced no ischaemic changes in an animal model in which the blood pressure was approximately 25 per cent lower than that in humans[12]. If the occlusion pressure exceeds 60 mmHg then the blood supply could fall to precarious levels. In two recent reports of the use of a circular cuff design around the upper anal canal in humans[31,32] intraluminal occlusion pressures of up to 85 and 70 mmHg respectively were applied. The results of the present study suggest that at these operating pressures the circular device could be unsafe if applied around the colon in the long term.

On inflation of the neosphincter there was a small but significant decrease in blood flow measured in the colon proximal to the device. This may occur because bowel is being angled and therefore obscured under the expanding sphincter. An alternative explanation is that as the resistance to blood flow increases by inflation of the expander there is a decrease in the total outflow past the device thereby decreasing the inflow of blood to the colon.

Erosion is recognized as one of the most serious complications of alloplastic implants placed around bowel. This may not be solely the result of ischaemia. Other factors contributing to erosion include infection and tissue reaction to the implant even if it is inert. The present study suggests that this neosphincter would reduce the likelihood of ischaemic effects on the bowel.

In conclusion, the results of the present study suggest that at the planned operating occlusion pressure of less than 45 mmHg the prosthetic anal sphincter should not risk the vascularity of the human colon, assuming that this has not been damaged at operation. Human implantation studies have now commenced with approval for the device from the Medical Devices Agency (London, UK).

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Prospective assessment of the hepatic perfusion index in patients with colorectal cancer

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Background This prospective study was designed to test the hypothesis that abnormal liver blood flow is related to poor prognosis in patients with colorectal cancer.

Methods The hepatic perfusion index (HPI), measured by dynamic hepatic scintigraphy, was assessed in 202 patients with colorectal cancer. Assessment for overt hepatic metastasis included liver palpation at laparotomy and perioperative computed tomography (CT). Follow-up at a dedicated clinic included regular abdominal ultrasonography and CT.

Results The HPI was abnormal (greater than 0·37) in 92 (88 per cent) of 105 patients with overt liver metastases. Of 89 patients with no evidence of overt metastases or residual tumour after primary resection, 52 had an abnormal and 37 a normal HPI. At a median follow-up of 39 (range 13–76) months, 25 of 38 patients with recurrnce had an abnormal HPI. Some 31 of 45 patients who died had an abnormal HPI. The HPI predicted overall recurrence ($P = 0·04$, log rank test). Multivariate analysis showed the HPI was independent of Dukes stage for predicting disease-free survival ($P = 0·04$, relative risk 1·94 (95 per cent confidence interval (c.i.) 1·03–3·67)) but this just failed to attain significance for overall survival ($P = 0·055$, relative hazard 1·88 (95 per cent c.i. 1·00–3·58)).

Conclusion The HPI predicts a poor outcome in patients with colorectal cancer and may be useful in patient selection for adjuvant chemotherapy.

Up to 25 per cent of all patients with colorectal cancer have overt liver metastases at presentation[1]. In addition, approximately 25 per cent of patients who undergo potentially curative resection of primary colorectal carcinoma have occult hepatic metastases which are impalpable at the time of initial surgery[2]. The hepatic perfusion index (HPI), which expresses the ratio of hepatic arterial to total liver blood flow, has been proposed as a possible method for detecting liver metastases in these patients.

First described by a group from Leeds[3], the HPI was used to assess liver blood flow in a cohort of patients with colorectal cancer. Abnormal values were found in 94 per cent of patients with overt liver metastases at the time of initial laparotomy[4]. Furthermore, of those who developed liver metastases within 3 years of primary resection, 87 per cent had abnormal liver blood flow, which suggested that HPI measurement could also identify the group of patients with occult liver metastases at presentation[5]. As a result, it was proposed that this might be a potentially useful test to allow better patient selection for adjuvant chemotherapy. However, the ability of the HPI to predict the appearance of metachronous liver metastases has not been fully substantiated.

The aims of this study were, first, to test the accuracy of the HPI, measured using dynamic hepatic scintigraphy, in identifying overt colorectal liver metastases and, second, to assess its potential as a screening test for occult liver metastases.

Patients and methods

Patient selection

All patients with colorectal cancer presenting between February 1990 and October 1994 were studied.

Hepatic assessment

Before laparotomy all patients underwent dynamic hepatic scintigraphy. Following an overnight fast, they were placed supine over a large field-of-view γ camera (400A or XC; General Electric Medical Systems, Milwaukee, Wisconsin, USA) fitted, with a high sensitivity parallel hole collimator and interfaced initially to a Link analytical MAPS (Gresham Scientific Instruments, Marlow, UK) and latterly to a Bartec Micas V (Park Medical, Farnborough, UK) computer. A rapid intravenous bolus of 80 MBq ^{99m}Tc-labelled albumin colloid was administered in a volume of 2 ml via an antecubital vein. Posterior images of the thorax and abdomen were recorded every 2 s for 2 min. From the resulting images, regions of interest were drawn around the liver and both kidneys, avoiding overlap with the lungs, aorta and spleen.

Time–activity curves for these regions were constructed and analysed using the left renal artery peak (Tp) to demarcate the hepatic arterial and portal venous components of the liver blood flow curve. From the liver curve, the gradients of the 8-s periods immediately before (G1) and after Tp (G2), excluding the frame immediately overlapping Tp, were calculated using least squares regression analysis. The HPI was expressed as the ratio of the hepatic arterial gradient to the sum of the hepatic arterial and portal venous gradients: $HPI = G1/(G1 + G2)$.

The HPI results were calculated as the mean of two complete reprocessings of each study, including redrawing regions of interest, by the same observer. The observers were blinded with respect to the identity of the patients during the processings in order to eliminate observer bias. The upper limit of normal using

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this technique has been reported[6] as 0·37, and this value was chosen as ethics committee approval to perform this study on normal controls had not been obtained.

Thorough liver assessment by inspection and manual palpation was performed at laparotomy. Lesions that were considered suspicious were biopsied if accessible. In addition, all patients underwent contrast-enhanced computed tomography (CT) of the liver in the perioperative period. Intraoperative ultrasonography was also performed in 40 patients but this did not identify any additional metastases which were not otherwise demonstrated by CT[7]. Patients who had suspected metastases on CT and who did not have a biopsy at laparotomy, either had CT or ultrasonographically guided needle biopsies or underwent serial CT looking for progression.

Patient follow-up

Patients with no initial evidence of liver or extrahepatic metastases were followed in a dedicated colorectal clinic. They were reviewed every 3 months for the first 3 years when clinical and ultrasonographic examinations were performed. Thereafter they were seen every 6 months. CT was performed on a yearly basis unless recurrence was suspected, when interval CT was undertaken. Hepatic recurrence was confirmed by fine-needle biopsy or progression on serial scanning. Locoregional recurrence was confirmed by endoscopic biopsy, fine-needle biopsy or, in the case of intra-abdominal nodal recurrence, progression on CT. Patients who died in hospital without previous evidence of liver metastases underwent autopsy if their relatives consented.

Statistical analysis

Tumour recurrence and survival was estimated with Kaplan–Meier life-table analysis and the log rank test. Multivariate analysis was also performed using stepwise regression (Cox proportional hazards model) to identify independent predictors of survival.

Results

A total of 212 patients was studied; 117 men and 95 women. Median age was 64 (range 36–92) years. Ten patients were excluded. Seven had unprocessable studies due to complete overlap between lung and liver (two patients) or poor bolus quality of the injected technetium (five). Two patients died in the immediate postoperative period and one was lost to follow-up. Of the remaining 202 patients, 105 had liver metastases at presentation. Eighty-nine patients had apparently curative resections of the primary tumour ('clear liver' group), while eight patients with locally advanced tumours underwent palliative resection or bypass only.

Relationship between hepatic perfusion index and disease status

Ninety-two (88 per cent) of the 105 patients with overt metastases at presentation had abnormal HPI values (greater than 0·37). Of the 89 patients in the 'clear liver' group, the HPI was abnormal in 52 (58 per cent) and normal in 37 (42 per cent). Median follow-up for survivors in this group was 39 (range 13–76) months. The relationship between HPI status and Dukes stage is shown in *Table 1*. Among the 'clear liver' group 12 patients (23 per cent) with abnormal HPIs and seven (19 per cent) with a normal HPI developed liver metastases, while 18 (35 per cent) with abnormal and ten (27 per cent) with normal HPI values developed locoregional recurrence. Overall, 25 patients (48 per cent) with abnormal HPIs developed recurrent disease while tumour recurred in 13 (35 per cent) of the 37 patients with normal HPI values. Ten patients died at home with unknown disease status: eight from unknown causes, one from myocardial infarction and one following a cerebrovascular accident. post-mortem examinations were not performed and consequently it is not known whether any had recurrent disease. One patient with a normal HPI died in hospital 2 months after resection. Post-mortem examination showed no evidence of recurrent disease.

Table 1 Relationship between Dukes stage and hepatic perfusion index status

	Abnormal HPI	Normal HPI
Dukes stage		
A	1 (2)	4 (11)
B	25 (48)	20 (54)
C	26 (50)	13 (35)
Total	52 (100)	37 (100)

Values in parentheses are percentages. HPI, hepatic perfusion index

Table 2 Relative hazard of disease recurrence or death and of death alone in the patients with a 'clear liver', estimated with the Cox proportional hazards model

	Dukes (C *versus* A/B)	HPI (abnormal *versus* normal)
Relative hazard of recurrence or death		
P	0·003	0·04
Point estimate	2·33 (1·32–4·11)	1·94 (1·03–3·67)
Relative hazard of death		
P	0·019	0·055
Point estimate	2·05 (1·13–3·73)	1·88 (1·00–3·58)

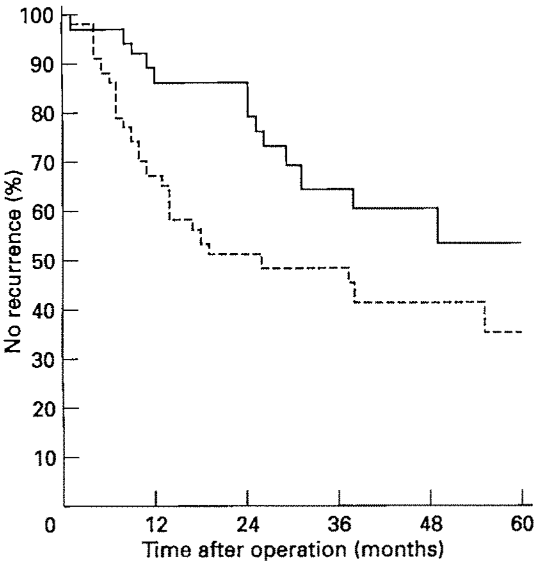
Values in parentheses are 95 per cent confidence intervals. HPI, hepatic perfusion index

Time to recurrence

In the 89 patients comprising the 'clear liver' group, the mean time to recurrence for those with normal and abnormal HPI was estimated with Kaplan–Meier life-table analysis. The ten patients who died with unknown disease status were excluded. When considered separately, there was no significant difference between the groups for time to liver recurrence or locoregional recurrence. The time to any recurrence, however, was significantly greater for the normal HPI group (mean disease-free time: normal HPI, 53 (95 per cent confidence interval (c.i.) 43–62) months; abnormal HPI, 38 (95 per cent c.i. 29–46) months; $P = 0·04$, log rank test) (*Fig. 1*).

Survival

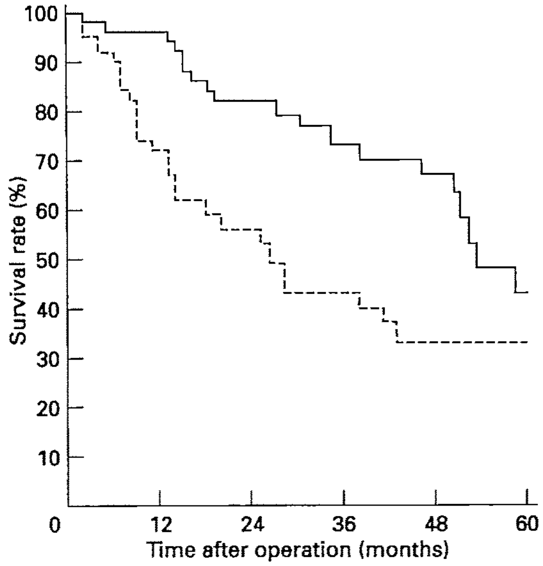
Forty-five of the 'clear liver' group died, of whom 31 had an abnormal HPI. Univariate analysis of disease-free survival as well as overall survival for the 'clear liver' group showed significantly better survival for patients with normal HPI status and Dukes stages A and B (*Figs 2* and *3*). Life-table analysis comparing normal to abnormal HPI stratified by Dukes stage (A/B *versus* C) showed a significant survival benefit for patients with normal HPI



No. at risk

Normal HPI	36	31	26	15	9	5
Abnormal HPI	43	29	20	14	9	3

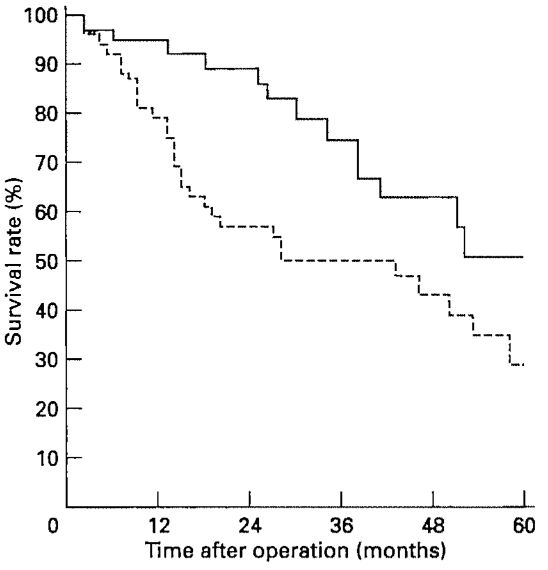
Fig. 1 Actuarial analysis of time to any recurrence in patients with normal (———) and abnormal (----) hepatic perfusion index (HPI). $P = 0{\cdot}04$ (log rank test)



No. at risk

A/B	50	48	38	24	17	8
C	39	28	18	14	7	3

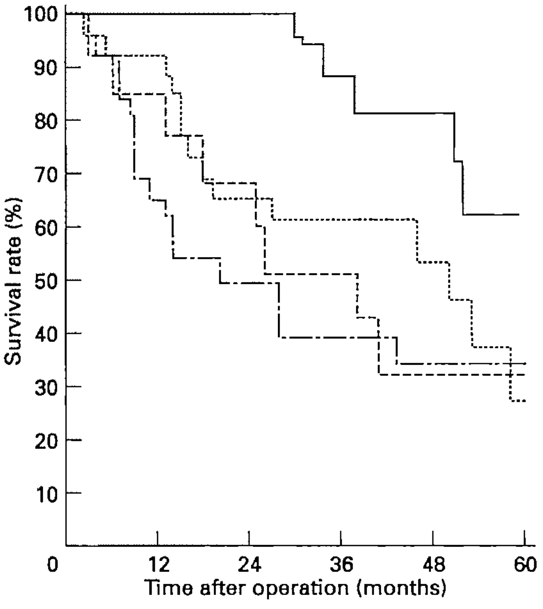
Fig. 3 Kaplan–Meier survival curves for patients with a 'clear liver' according to Dukes stage: ———, stage A/B; ----, stage C. $P = 0{\cdot}0048$ (log rank test)



No. at risk

Normal HPI	37	35	29	20	12	7
Abnormal HPI	52	41	27	18	12	4

Fig. 2 Kaplan–Meier survival curves for patients with a 'clear liver' according to hepatic perfusion index (HPI) status: ———, normal HPI; ----, abnormal HPI. $P = 0{\cdot}0165$ (log rank test)



No. at risk

Normal HPI, A/B	24	24	21	14	10	5
Normal HPI, C	13	11	8	6	2	2
Abnormal HPI, A/B	26	24	16	10	7	2
Abnormal HPI, C	26	17	10	7	5	1

Fig. 4 Kaplan–Meier survival curves for patients with a 'clear liver' stratified by Dukes stage and hepatic perfusion index (HPI): —, normal HPI, stage A/B; – – –, normal HPI, stage C; ·····, abnormal HPI, stage A/B; —·—·—, abnormal HPI, stage C. $P = 0{\cdot}005$ (normal HPI, stage A/B *versus* abnormal HPI, stage A/B), $P = 0{\cdot}925$ (normal HPI, stage C *versus* abnormal HPI, stage C) (log rank test)

and stage A and B primary tumours. Conversely there was no difference in survival between the normal and abnormal HPI groups with Dukes C primaries (*Fig. 4*).

Multivariate analysis identified both Dukes stage and HPI status as independent predictors of disease-free survival (Dukes stage (C *versus* A/B), $P = 0{\cdot}003$, point estimate 2·33 (95 per cent c.i. 1·32–4·11); HPI (abnormal *versus* normal), $P = 0{\cdot}04$, point estimate 1·94 (95 per cent c.i. 1·03–3·67)). Dukes stage was also a significant independent predictor of mortality, whereas the HPI just fell short of achieving significance at the 95 per cent confidence level as an independent predictor of death (Dukes stage (C *versus* A/B), $P = 0{\cdot}019$, point estimate 2·05 (95 per cent c.i. 1·13–3·73); HPI (abnormal *versus* normal), $P = 0{\cdot}055$, point estimate 1·88 (95 per cent c.i. 1·00–3·58)) (*Table 2*).

Discussion

Although an association between overt hepatic metastases and abnormal liver blood flow is well established[4,8,9], the suggestion that the HPI can detect occult liver deposits accurately has previously been the subject of debate[9–12]. A study from France[13] has supported the Leeds data. Abnormal HPI was present in 12 of 13 patients who developed metachronous hepatic metastases within 2 years of follow-up[13]. However, the sensitivity for patients with overt liver metastases was only 73 per cent. In both studies the specificity was low: 70 and 34 per cent for the Leeds and French groups respectively.

On first inspection these results appear disappointing. While they confirm the HPI as a sensitive test for detecting overt liver metastases, the results for occult liver metastases suggest that it is of little use for their identification. If the HPI is to be of any practical value it must be assessed as a means of identifying patients with truly occult metastases, i.e. those not visible with conventional imaging methods. The two previous studies relied on laparotomy findings alone to confirm metastases at presentation, but this lacks sensitivity[2] and many patients with overt metastases detected by CT in this study would have been included in the occult metastases groups in the former series. It is therefore not surprising that the accuracy for occult tumours was lower. Despite the poor sensitivity for detecting occult liver metastases, survival was worse for patients with an abnormal HPI. This apparent anomaly is probably explained by the ten patients (nine of whom had an abnormal HPI) who died with unknown disease status and who were excluded from the recurrence analysis. It is possible that a proportion of these patients had metastatic disease which remained undetected and that the true incidence of tumour recurrence in the abnormal group is therefore underestimated.

Both univariate and multivariate analysis demonstrated a disease-free survival benefit for patients with a normal HPI. An overall survival advantage for normal HPI was also apparent on univariate analysis, but this was confounded by Dukes stage when the Cox proportional hazards model was applied. Disease recurred sooner in the abnormal HPI group although this was significant only when both liver metastases and locoregional recurrence were considered together. This connection between abnormal HPI and locoregional metastasis is of interest as liver blood flow changes have not previously been associated with local recurrence. While the mechanism for this is unknown, the implication is that either residual local tumour had a direct effect on hepatic blood flow or patients with local recurrence and abnormal HPI values also had occult liver metastases which remained undetected.

The underlying mechanisms for the hepatic haemodynamic changes have been the subject of previous research[14–18]. Evidence obtained from a rat model of liver metastasis suggests that a circulating vasoconstrictor is responsible for the increased splanchnic vascular resistance and subsequent reduction in portal venous flow[19]. Whatever the underlying mechanisms, the fact that the HPI predicts tumour recurrence *per se* is of clinical significance because these patients might be suitable candidates for adjuvant therapy.

There is strong evidence that patients with Dukes C carcinomas should receive adjuvant chemotherapy[20], but doubt concerning the benefit of this treatment still exists for those with early stage tumours. The survival data for the HPI groups stratified by Dukes stage show that the only significant difference was between patients with normal HPI and Dukes stage A/B tumours and those with abnormal HPI and stage A/B lesions. This suggests that the HPI may be of value for identifying patients with early tumours who do badly and who might benefit from adjuvant chemotherapy. Conversely, patients with normal HPI values and early stage tumours might be spared unnecessary treatment. This conclusion remains somewhat speculative because of the relatively small numbers in this subgroup analysis. To test it properly would require a randomized clinical trial, the establishment of which would be difficult to justify on the basis of this evidence alone. An alternative approach could be HPI assessment in patients with Dukes B tumours before entry into an ongoing trial of adjuvant chemotherapy such as the QUASAR (Quick And Simple And Reliable) study[21], which includes a no-treatment arm. Survival differences between treatment and no-treatment groups could then be compared.

In conclusion, this study shows that, despite being apparently weak at identifying occult liver metastases, an abnormal HPI is associated with poor outcome in patients having potentially curative resection for colorectal cancer. If used in conjunction with tumour staging, the HPI might be useful in selecting patients for adjuvant chemotherapy.

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Ultrasonographically-guided fine-needle aspiration cytology in the diagnosis of colonic lesions

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Background The use of fine-needle aspiration cytology (FNAC) in the diagnosis of colonic lesions was investigated.

Methods Some 22 patients (median age 71 years) with a colonic lesion identified on abdominal ultrasonography underwent ultrasonographically-guided FNAC using a 21-G needle. The sample was checked immediately by a cytopathologist for adequacy.

Results Eighteen patients had colonic carcinoma; aspiration cytology detected malignant epithelial cells consistent with colonic carcinoma in 17 patients and severely dysplastic cells in one patient. The sensitivity and specificity of ultrasonographically-guided FNAC in the diagnosis of colonic carcinoma was 94 and 100 per cent respectively. The remaining four patients had a diagnosis of ileocaecal tuberculosis, ileocaecal Crohn's disease, and metastatic adenocarcinoma in the liver with no identifiable primary (two patients). One demonstrated granulomata, grew acid-fast bacilli and the patient was treated for tuberculosis. One had inflammatory cells and the patient was found to have Crohn's disease on histology. The remaining two patients had confirmed metastatic adenocarcinoma in the liver on aspiration cytology but suspected colonic lesions were found to be benign on cytological examination and no primary lesion was subsequently demonstrated. There were no complications of FNAC and patients complained of minimal discomfort. There has been no evidence of tumour recurrence with a median follow-up of 12 (range 1–25) months.

Conclusion Ultrasonographically-guided FNAC is a valid method for the diagnosis of colonic tumours.

Ultrasonographically-guided fine-needle aspiration cytology (FNAC) is a well established method for the diagnosis of intra-abdominal tumours, either using transabdominal ultrasonography[1] or endosonography[2], with high sensitivity and specificity and a low complication rate. This may be applied to oesophageal, gastric, pancreatic, hepatic or biliary lesions[1–5]. Abdominal ultrasonography has been reported to be accurate in the diagnosis of several colonic conditions[6] including the site and nature of obstructing lesions[7], colitis[8], diverticulitis[9] and cancer[10,11]. Colonic tumours can be identified by abdominal ultrasonography with high sensitivity and moderate specificity[12]. Colonic biopsies for histological diagnosis are usually obtained by colonoscopy but total colonoscopy may be technically impossible even in the best hands, and is only reliably achieved in 70 per cent of patients in all units[13]. The aim of this study was to assess use of ultrasonographically-guided FNAC in the diagnosis of colonic masses.

Patients and methods

Twenty-two patients (six men) with a median age of 71 (range 22–87) years were recruited following identification of colonic pathology on abdominal ultrasonography (two ileocolic, 11 right colon, three transverse colon, six left colon). The majority of patients comprised a group referred with a high suspicion of colonic malignancy from the history, routine examination and investigations. The radiologist and cytologists were blinded to the diagnosis, if already confirmed, in all cases. One patient had a suspected recurrence of a colonic tumour in the bowel wall. Written consent for abdominal FNAC was obtained from all patients.

Ultrasonographically-guided FNAC was performed using an ATL (HDI) 3000 machine (Advanced Technology Laboratory, Camden, New Jersey, USA) with a C4–2 broadband width probe. Routine abdominal ultrasonography was undertaken by a single radiologist with the addition of views of the oesophagus, stomach and the entire colon where technically feasible. Limited views of the rectum were undertaken as it was felt that this area could be viewed, and lesions biopsied, satisfactorily by sigmoidoscopy. Fine-needle aspiration of the colonic mass was performed by the radiologist using a 21-G non-cutting needle under ultrasonographic guidance through a scalpel stab in the skin. The aspirate obtained was checked immediately by a consultant cytopathologist for adequacy, and repeated if considered to be of inadequate cellularity. Up to three passes only were made on each patient to obtain adequate cytology and no patient underwent repeat cytology at another sitting. Of the 22 patients, adequate cytology was obtained in all patients and on a single pass in 18 of them. This procedure was performed as an outpatient procedure unless the patient was already an inpatient. No antibiotics were given to cover the procedure. Six of the patients had liver metastases confirmed on ultrasonography at the same examination.

Four direct preparations were made from the fine-needle aspirate, either air-dried or alcohol fixed, and the residual sample rinsed into Hanks balanced salt solution to allow further cytospin preparations to be made. Direct air-dried slides were stained with Hema-Gurr (rapid Giemsa stain) and assessed immediately in the ultrasonography room. Slides were subsequently stained with May–Gruenwald Giemsa or Papanicolaou stains for definitive cytological diagnosis. The slides were reported by one of two cytopathologists. The cytology was compared with definitive histology if obtained, and with the final patient diagnosis.

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Results

Eighteen of the 22 patients had colonic carcinoma. FNAC in 17 of these patients demonstrated malignant epithelial cells consistent with colonic carcinoma. The cytology of the remaining patient with colonic carcinoma was reported as severely dysplastic and highly suspicious of a malignant tumour. The sensitivity and specificity of ultrasonographically-guided FNAC in the diagnosis of colonic carcinoma was 94 and 100 per cent respectively.

The diagnosis of the remaining four patients was ileocaecal Crohn's disease in one, caecal tuberculosis in another, and liver metastases confirmed on FNAC but no confirmed primary in the remaining two patients.

FNAC of the patient with tuberculosis demonstrated granulomata and culture of part of the aspirate grew acid-fast bacilli which were consistent with *Mycobacterium tuberculosis*. The patient was treated successfully for tuberculosis and improved with treatment. Cytological examination of samples from the patient with Crohn's disease demonstrated inflammatory cells and the diagnosis was confirmed histologically following resection of an ileocolic stricture. The remaining two patients had confirmed metastatic adenocarcinoma in the liver on FNAC. The suspected colonic masses were subjected to FNAC and reported to contain benign cells only. One patient underwent a partial gastrectomy for gastrointestinal haemorrhage and histology of the specimen demonstrated adenocarcinoma in the retroperitoneal lymph nodes but no primary was found in the stomach nor could any tumour be detected in the abdomen at laparotomy, other than the liver metastases. No primary lesion could be detected in the other patient and the colon was normal on colonoscopy.

There were no acute complications of FNAC and the patients complained of minimal discomfort. The median follow-up after FNAC was 12 (range 1–25) months. No patient with carcinoma has had a recurrence of the malignancy and there have been no long-term complications.

Discussion

Ultrasonographically-guided FNAC has been shown to be an extremely useful procedure for the diagnosis of abdominal tumours and its application has been extended with the use of endoscopic ultrasonography which, by placing the transducer closer to the area of interest, allows greater resolution. A recent study[2] using endosonography has shown that lesions in the gastrointestinal wall can be biopsied with a high degree of accuracy, with the site of the lesion including the oesophagus, stomach, duodenum and rectum, but not the colon. It is possible to detect colonic tumours with a high degree of sensitivity, but only a moderate specificity[12]. Extension of this technique by the addition of FNAC should improve the specificity and it would be reasonable to proceed to surgery with a cytological diagnosis of a colonic malignancy. In some cases, additional diagnostic information can be obtained; in one patient in this study ultrasonography demonstrated a localized pericolic abscess adjacent to a sigmoid tumour from which pus could be aspirated, confirming a localized perforation of the tumour.

Colonoscopy and/or barium enema are the usual methods for identification of colonic tumours and provide good resolution of the whole bowel, so the role of an alternative diagnostic method which does have potential complications requires careful evaluation. Barium enema may provide a potential diagnosis but cannot provide cytological or histological confirmation of the diagnosis and may fail if the patient has insufficient sphincter control to retain the barium. Colonoscopy can provide direct visualization of a colonic tumour and histological confirmation of the diagnosis. However, both colonoscopy and barium enema require an empty bowel, necessitating the use of bowel preparation, which may produce fluid and electrolyte imbalance particularly in elderly patients, and are unpleasant. It may be difficult to traverse the whole colon in elderly patients and this may prove impossible in up to 30 per cent of patients[13]. The demand for and cost of colonoscopy must also be considered as neither are insubstantial. Ultrasonographically-guided FNAC requires no bowel preparation and can provide a definite diagnosis. Although histological or cytological confirmation of the diagnosis is not essential in every case, it will aid clinical decision making and management in the majority of cases. The radiologist involved in this study was an experienced ultrasonologist but colonic views from abdominal ultrasonography are usually ignored and expertise in detecting bowel pathology could be acquired easily. The presence of an experienced cytopathologist at the time of FNAC is invaluable to ensure adequacy of the aspirate and the efficiency of the procedure, minimizing the number of needle passes required and false-negative diagnoses.

FNAC appears accurate in the diagnosis of colonic masses but does have potential complications such as haemorrhage, sepsis and seeding of malignancy. A European study of over 10 000 ultrasonographically-guided abdominal fine-needle aspiration biopsies reported a mortality rate of 0·018 per cent, both deaths resulting from haemorrhage following biopsy of the liver[14]. An American study[15] reported five deaths after 16 381 fine-needle aspiration biopsies (0·031 per cent). The same paper reviewed the literature and reported a total of 33 deaths following abdominal fine-needle aspiration biopsy. Twenty-one of these were after liver biopsies, 17 due to haemorrhage, and six after pancreatic biopsies, five due to pancreatitis. None occurred following colonic biopsy but this procedure is performed much less frequently. In the present study, there were no acute complications and no evidence of septic events.

Needle-tract seeding of malignancy can occur following abdominal fine-needle aspiration biopsy. A review in 1991 of all published cases of needle-tract seeding reported 23 cases, 11 of these following pancreatic biopsy[15]. The reported frequency was between 0·003 and 0·009 per cent. In almost half of these cases, however, a needle larger than 21 G was used, giving core biopsies rather than cytological material. Only a single case of needle-tract recurrence following needle aspiration biopsy of a colonic carcinoma has been reported[16]; this was performed using a 20-G needle. The majority of needle-tract recurrences following abdominal fine-needle aspiration biopsy are noted within 6 months of the procedure[15] and the majority of recurrences of colonic carcinoma following surgery alone are within the first 2 years of surgery[17]. The median duration of follow-up in this study was 1 year; 14 of the patients with carcinoma have been followed up for more than 6 months after the FNAC and there have been no tract recurrences.

Ultrasonographically-guided FNAC is a valid method for the diagnosis of colonic tumours. There were no acute complications in this study and there has been no evidence of needle-tract seeding in cases of aspiration of malignant tumours. Ultrasonographically-guided FNAC is not a substitute for colonoscopy and biopsy but may be useful in the diagnosis of difficult or elderly patients.

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Quality of life in patients with benign anorectal disorders

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Background Benign proctological conditions are very common in Western civilization. However, to date quality of life in these patients has not been evaluated comprehensively. The aim of this study was to investigate whether the Gastrointestinal Quality of Life Index (GIQLI) is a useful instrument for measuring quality of life in these patients, and subsequently to establish baseline values for different anorectal disorders.

Methods The questionnaire was completed by 325 consecutive patients (182 men; mean age 49 years) seen at the proctology outpatient clinic. For further analysis patients were classified into nine subgroups according to the primary diagnosis: group 1, haemorrhoids ($n = 96$); group 2, anal fissure ($n = 38$); group 3, fistula *in ano* ($n = 22$); group 4, severe constipation ($n = 14$); group 5, faecal incontinence ($n = 35$); group 6, symptomatic anterior rectocele ($n = 12$); group 7, perianal abscess ($n = 7$); group 8, perianal thrombosis ($n = 7$); and group 9, miscellaneous conditions (e.g. skin tags, anal papillomas, mild constipation, rectal polyps) ($n = 94$). The GIQLI scores were compared between the subgroups. In addition the GIQLI scores of age-matched healthy controls, derived from data in the literature, were compared with the patients' scores.

Results The mean GIQLI score for all patients was 113 (78·5 per cent of the maximum score of 144). Mean scores for the nine diagnostic subgroups were: group 1, 120; group 2, 104; group 3, 119; group 4, 94; group 5, 93; group 6, 112; group 7, 115; group 8, 129; and group 9, 117. Age-matched controls from a series published previously had a significantly higher GIQLI score compared with all patients ($P < 0{\cdot}0001$). However, only the subgroups of patients with miscellaneous conditions, fissures, severe constipation and faecal incontinence had a significantly poorer quality of life than age-matched healthy individuals.

Conclusion The GIQLI is a valuable instrument for measuring quality of life in patients with benign anorectal disorders. Although certain diseases do not seem to affect quality of life profoundly, certain subgroups of patients, most notably those with incontinence and severe constipation, are extremely compromised. Severely constipated individuals exhibit the same poor quality of life as patients with faecal incontinence.

Quality of life and the need for its practical clinical application have become important issues in all medical disciplines[1]. It is also increasingly perceived as a significant factor in the management of surgical patients as there is a growing awareness among physicians as well as patients of the need to integrate aspects of functional and psychosocial impairment in medical care[2]. Surgeons dealing with patients suffering from anorectal diseases know that their well-being is often compromised. While this might be more obvious in patients with faecal incontinence it also holds true for commoner disorders, such as haemorrhoids or fistula *in ano*. Patients often complain about troublesome symptoms interfering with daily life. Furthermore, medical attention is frequently delayed because of fear of malignancy and/or embarrassment. To the authors' knowledge there have been no reports of quality of life in patients with benign proctological diseases. The aim of this study was first to evaluate whether the Gastrointestinal Quality of Life Index (GIQLI) developed by Eypasch and co-workers[3] is a valuable instrument for measuring quality of life in these patients, and subsequently to establish baseline values for various proctological entities.

Patients and methods

At the proctology outpatient clinic in this department, 325 consecutive patients (182 men; mean(s.d.) age 49(13) (range 17–83) years) with various anorectal diseases were asked to complete the German version of the GIQLI questionnaire[4] at their first visit. Patients were classified into following nine subgroups: group 1, haemorrhoidal disease ($n = 96$); group 2, anal fissure ($n = 38$); group 3, fistula *in ano* ($n = 22$); group 4, severe chronic constipation (defined as one or fewer bowel movements per week and/or a pathological transit study) ($n = 14$); group 5, faecal incontinence ($n = 35$); group 6, symptomatic anterior rectocele ($n = 12$); group 7, perianal abscess ($n = 7$); group 8, perianal venous thrombosis ($n = 7$); and group 9, minor miscellaneous conditions (e.g. skin tags, anal papillomas, rectal polyps, mild constipation, non-specific proctitis, descending perineum syndrome) ($n = 94$). In the case of two or more anorectal pathologies (e.g. haemorrhoids and severe chronic constipation) the more severe diagnosis (in this case severe chronic constipation) was chosen as the main disorder.

The GIQLI questionnaire comprises 36 multidimensional items covering symptoms, and physical, emotional and social dysfunction related to gastrointestinal diseases or their treatments. Each item scores from 0 to 4 points. The GIQLI score is calculated by simple addition of all item scores so that an overall score of 0 would constitute the worst, while a score of 144 represents the best possible result.

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Patient assessment comprised a standardized proctological history, abdominal examination, digital rectal examination as well as proctoscopy and rectosigmoidoscopy in all patients. Depending on the working diagnosis, colonoscopy, barium studies (enema and/or defaecography), colonic transit using radio-opaque markers, endosonography and anorectal manometry were also performed.

The mean GIQLI score of all patients as well as of each subgroup was compared with that of a cohort of 150 healthy individuals with a mean age of 48 (range 18–74) years (mean(s.d.) GIQLI score 121(15)), as published in the original paper by Eypasch *et al.*[4].

Statistical analysis

Differences between the subsets of patients were analysed with the Mann–Whitney U test. Differences between age-matched controls and patients were examined using an approximation of the unpaired Student t test for unequal standard deviations. Compared with the standard Student t test this modification gives more conservative estimates. $P<0\cdot05$ was regarded as significant for both tests.

Results

The mean score for all patients was 113 (78·5 per cent of the best possible score of 144). The results for the nine diagnostic subgroups are shown in *Table 1* and *Fig. 1*. Differences in the GIQLI score were significant for incontinent and for chronically constipated patients when tested against all other patient subgroups. However, quality of life did not differ between incontinent and constipated patients ($P=0\cdot85$).

The mean GIQLI scores for the whole group of patients and for the groups with miscellaneous conditions, fissures, severe constipation and incontinence were also significantly different from that of an age-matched control group, derived from data by Eypasch and co-authors[4]. Because of the small number of patients, statistical analysis was not possible for patients with perianal venous thrombosis or abscess. However, patients with haemorrhoids, fistula *in ano* and symptomatic rectocele did not differ significantly from age-matched controls with regard to their overall quality of life (*Table 1*).

Table 1 Gastrointestinal Quality of Life Index scores in patient and control groups

Diagnosis	n	GIQLI score*	P‡
Controls	150	121(15)	—
Perianal thrombosis	7	129(10)	n.a.
Haemorrhoids	96	120(14)	n.s.
Fistula *in ano*	22	119(18)	n.s.
Miscellaneous conditions†	94	117(15)	0·048
Perianal abscess	7	115(12)	n.a.
Symptomatic rectocele	12	112(14)	n.s.
Anal fissure	38	104(19)	<0·0001
Severe constipation	14	94(15)	<0·0001
Faecal incontinence	35	93(21)	<0·0001
Total (patients)	325	113(19)	<0·0001

*Values are mean(s.d.). †For example, eczema, skin tags, papillomas, rectal polyps, minor constipation, non-specific proctitis, descending perineum syndrome. GIQLI, Gastrointestinal Quality of Life Index; n.a., not applicable; n.s., not significant. ‡*Versus* age-matched controls (mean age 48 years), derived from data published by Eypasch *et al.*[4] (approximated Student t test for unequal standard deviations)

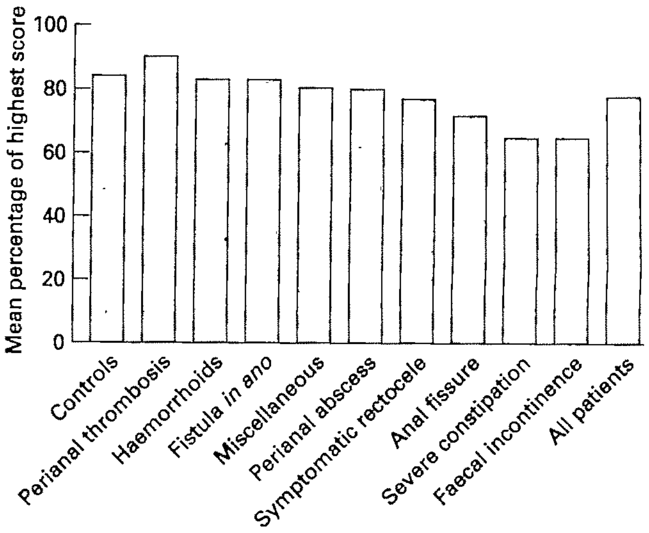

Fig. 1 Distribution of the mean Gastrointestinal Quality of Life Index (percentage of the highest possible score). Controls were age-matched healthy individuals with a mean age of 48 years (Eypasch *et al.*[4])

Discussion

Measurement of quality of life in patients with various medical conditions is used to evaluate the nature and extent of functional and psychosocial impairment. Furthermore, it allows the monitoring of quality of care and comparison of different therapeutic approaches[1]. Measuring quality of life necessitates use of instruments that are consistent, reproducible, sensitive and applicable[5]. To date the GIQLI, first published in the German version in 1993[4], is the only validated tool to assess quality of life in patients with malignant and benign gastrointestinal disorders. Although the authors state that the preliminary questionnaire was also completed by patients suffering from diseases of the rectum and anus (among others with oesophageal, gastric, pancreatic, hepatobiliary, and small and large intestinal disorders) there is no detailed information given on the number of patients with anorectal disease and the specific diagnoses[4]. The final version of the GIQLI, as used in the present study, was tested on 194 patients undergoing laparoscopic cholecystectomy and on 25 patients with various stable gastrointestinal diseases[3].

Despite the fact that benign proctological conditions, such as haemorrhoids, fistula *in ano*, constipation, incontinence and many others, are common in Western civilization, there are few studies dealing with the quality of life of these patients. Most research in the field of quality of life seems to focus on oncological aspects[6–9] or specific conditions, such as inflammatory bowel disease[10–12], ileoanal pouch procedures[13–15] or pancreatitis[16].

The present study therefore tried to establish whether the GIQLI is a valuable instrument for measuring quality of life in patients with benign anorectal diseases in an outpatient setting. As patients with acute anorectal conditions, such as abscess or perianal venous thrombosis, usually present as emergency cases and not during the weekly proctology clinic, these diseases are somewhat under-represented in this study. In the absence of a contemporary age-matched control group, the patient data were compared with those of a control group described in the original study by Eypasch *et al.*[4]; this group comprised 150 healthy individuals with a mean age of 48 years, which matched the age of the authors' patients and could therefore be used as a reference. Significant differences between age-matched controls and patients were noted for some of the subgroups, most notably for patients with incontinence and severe constipation. However, direct comparison of healthy subjects with patients poses problems as relevant domains (symptoms, psychosocial function, etc.) are perceived quite differently in the various groups[17,18].

As might be expected, the present data indicate that comparatively minor problems, such as haemorrhoids, anal papillomas, skin tags and the descending perineum syndrome, do not seem to have a significant impact on the overall quality of life. Certain chronic conditions, such as fistula *in ano* and symptomatic rectocele, are also relatively well tolerated, which could be explained by an adaptation process during the course of the disease. However, it is difficult to interpret the difference in GIQLI score between patients with the two acutely presenting conditions, perianal venous thrombosis and anal fissure. It could be argued that patients with a painful perianal thrombosis present more or less immediately after experiencing symptoms. As all items in the GIQLI always relate to the 2 weeks before questioning there might have been little disruption in the patient's well-being apart from the anal pain experienced.

As might be expected, faecal incontinence has a profoundly negative impact on overall quality of life. This compares well with the results of a study by Sharpe and co-workers (median score 102 in 15 patients with faecal incontinence)[19], which to the authors' knowledge is the only study using the GIQLI in patients with anorectal disease. Other investigators have shown that family life, specifically with respect to sexuality, and employment are the two aspects most affected in the quality of life of individuals suffering from incontinence[20]. It is interesting to note that severe chronic constipation is equally distressing for the patients concerned. Although a symptom primarily studied in the elderly[21,22], slow transit constipation is a poorly understood disease affecting almost exclusively middle-aged women[23]. Indeed, a recent study showed a good or improved quality of life in 90 per cent of 74 patients who had undergone subtotal colectomy and ileorectostomy for this disorder[24]. As this operation is a very radical therapeutic option, it underlines the severity of the condition with regard to the quality of life in these patients.

It should be emphasized that the GIQLI is not a diagnostic tool as it does not discriminate between different diseases. As other investigators[3] have shown, large variations were observed in the GIQLI score for patients with the same diagnosis. A low index score could be due to troublesome symptoms which were coped with adequately from a psychosocial point of view, or relatively minor symptoms combined with a negative, depressive reaction[4]. This may explain the equally severe scores in patients with disparate conditions such as incontinence and severe constipation.

It is concluded that the GIQLI is a valuable instrument for measuring quality of life in patients with benign anorectal disorders. Although certain diseases do not seem to affect quality of life profoundly, certain subgroups of patients, most notably those suffering from incontinence and severe constipation, are severely compromised. In this context it is interesting to note that severely constipated individuals exhibit the same poor quality of life as patients with faecal incontinence.

Acknowledgements

The authors thank Dr I. Haubitz of the Department of Statistics and Dr M. Fein of the Department of Surgery, University of Würzburg, for help with the presentation and statistical interpretation of the data.

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British Journal of Surgery 1998, 85, 1720–1722

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Role of magnetic resonance angiography for assessment of abdominal aortic aneurysm before endoluminal repair

Sir

We read with interest the study by Nasim *et al.* (*Br J Surg* 1998; 85: 641–4) but have concerns that the authors' conclusions are not supported by the data presented.

First, one-quarter of the patients who had magnetic resonance angiography (MRA) and computed tomography (CT) did not have colour duplex imaging, and more than one-half did not undergo intra-arterial digital subtraction angiography. These omissions surely weaken the comparison. Second, the importance of accurate proximal and distal neck measurements are emphasized in the discussion but no objective data or interobserver/intraobserver correlations are provided. In addition, any comparison between colour duplex imaging and any other modality is difficult as the duplex examination can only reasonably be interpreted by the operator. It is not clear from the paper how these comparisons were made.

Spiral CT angiography with image reconstruction has been proposed as the method of choice for the assessment of endoluminal abdominal aortic aneurysm (AAA) repair[1–3], and is the preferred modality in our centre. In a recently reported study MRA and spiral CT were found to be equal in evaluating the proximal extent of the AAA and in measuring all aortic dimensions[4]. Unfortunately, spiral CT was not used as a comparison by Nasim *et al.* The assessment of AAA before endoluminal repair requires precision and is essential for a successful endoluminal procedure. MRA may be the modality of choice, but more objective comparisons are required before CT can be dismissed as inferior.

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Authors' reply

Sir

Thank you for the opportunity to reply. The primary objective of the study was to ascertain which of the non-invasive imaging modalities (CT, MRA and colour duplex imaging) was superior in assessing aneurysm morphology in the context of endovascular aneurysm repair. Angiography is an invasive procedure and was only undertaken in patients with favourable anatomy using the above three modalities. Only 55 of the 77 patients underwent colour duplex examination. This represents one of the largest series in a study of this kind[1,2] and does not significantly affect the validity of the comparison. Colour duplex imaging is operator-dependent and comparison with other modalities can be difficult. All examinations in the study were performed by a single vascular technician using a pro forma containing the parameters included in the comparison. Visualization (or the lack of it) was noted as well as the absolute measurements. Objective data on the various aneurysm parameters were included in the original manuscript but excluded after editorial review because of space limitations.

Our study commenced in January 1994 when spiral CT was not in widespread use and therefore not included in the comparison. Our paper highlights some of the limitations of conventional CT but does not dismiss spiral CT as an inferior modality. We have proposed MRA as a suitable alternative imaging modality that does not involve the use of ionizing radiation.

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Cytogenetics and the surgeon: an invaluable tool in diagnosis, prognosis and counselling of patients with solid tumours

Sir

We read with interest the informative review by Humphrey *et al.* (*Br J Surg* 1998; 85: 725–34) of the increasingly important subject of cancer genetics as applied to surgical practice. However, we feel that some points need clarification.

Gardner and Richards[1] described the association between familial adenomatous polyposis (FAP) and epidermoid cysts, osteomas and 'fibromas', later found to be desmoid tumours. The term 'Gardner's syndrome' was only later used to describe colorectal polyposis occurring with these extra-colonic manifestations[2]. An excess of upper gastrointestinal, adrenal and papillary thyroid neoplasms, as well as hepatoblastoma, occurs with FAP3', but these do not form part of Gardner's original syndrome. While FAP has intriguing and complex genotype–phenotype correlations, Gardner's syndrome is now considered to be genetically indistinct from FAP[4], and systemic examination has revealed that most patients with FAP have at least one feature of the syndrome[5,6]. Although it is of historical interest, the term 'Gardner's syndrome' is no longer considered a genetic or clinical entity and should be regarded as obsolete[3].

Recent molecular genetic investigation of Turcot's syndrome[7], the association between colorectal adenomatous polyposis and central nervous system tumours, has shown that approximately two-thirds of families have mutations in the *APC* gene, with cerebellar medulloblastoma as the predominant brain tumour. Most of the families in the remaining third, including Turcot's original family, appear to have variants of hereditary non-polyposis colorectal cancer with glioblastoma as the predominant brain tumour. This illustrates how one syndrome can be cuased by mutations in more than one gene, the phenomenon of genetic heterogeneity.

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Venous insufficiency and perforating veins

Sir

Bergan in his leading article (*Br J Surg* 1998; 85: 721–2) is correct in saying that incompetent perforating veins are doubly deleterious. There are now well documented biomedical effects that have previously been reported. Recent research suggests that perforating veins and their associated fascial defects allow the intravascular forces generated by posture and exertion to strain the overlying skin. This strain in turn causes capillary distortion and a paradoxical decrease in the skin nutritional blood flow (*Fig. 1*)[1].

This is the reason that treating perforators and wearing support helps. Treatment of perforating veins reduces the capillary distortion as well as improving calf pump efficiency.

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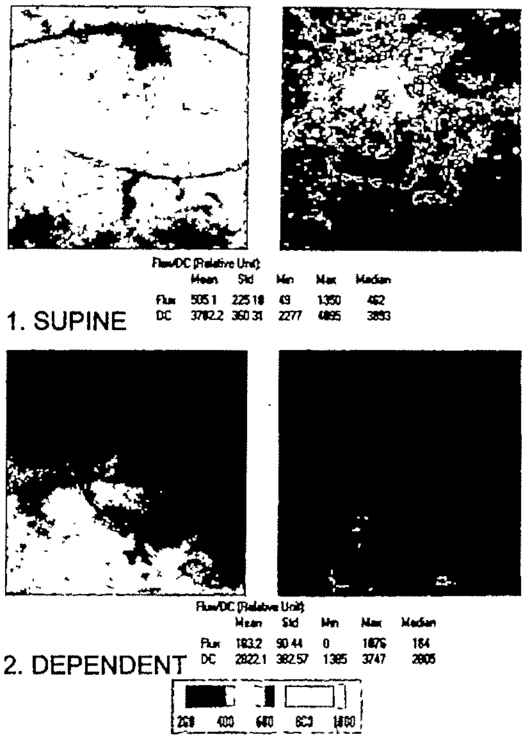

Fig. 1 Varicose vein laser Doppler images. Ares of interest taken as that enclosed by the black pen marks. Mean flux decreases from 505 to 183 perfusion units after lowering limb to the floor, i.e. 36 per cent of baseline value

Arteriovenous fistula using transposed basilic vein

Sir

We read with interest the paper by Butterworth *et al.* (*Br J Surg* 1998; 85: 653–4) on basilic vein transposition for dialysis access. Based on our own recent experience of providing dialysis access in a new renal unit we have used this technique in 11 patients in the past 2·5 years with good results. Butterworth *et al.* make a good point that a synthetic graft may be used after vein transposition has failed, but not the other way round.

It is worth making the following points: (1) a brachiobasilic graft is a durable and reliable form of access[1] and, in patients with reduced life expectancy, may be the most appropriate. Our patients had a mean age of 66 years when referred for vascular access and a mortality rate of 33 per cent at 1 year. It may be difficult, even in the long term, to demonstrate a significant difference between the two procedures in such a population; (2) vein transposition is a bigger operation and may take twice as long as an interposition graft; and (3) synthetic grafts can be cannulated significantly earlier[2], which is an advantage in sick patients with failed access and neck line problems.

While we agree that the transposition technique is useful we do not agree that it should always be used before resorting to prosthetic grafts.

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Assessment of a scoring system for breast imaging

Letter 1

Sir

The paper by Roche *et al.*[1] (*Br J Surg* 1998; 85: 669–72) describes a scoring system for breast imaging and combines this with the results of aspiration cytology to determine the positive predictive value of this combination in making a diagnosis of breast cancer. During the period 1994–1997 the St Marys Hospital Breast Group in London used this system with similar results. We added to this grading system two additional prefixes, 'GP' and 'S'. This was to allow the general practitioner (GP) and the surgeon (S) to give their impressions with regard to suspicion of malignancy in women presenting with breast lumps. The 1–5 system was used with increasing suspicion of cancer associated with increasing number. Thus, GP5 indicates that the GP believes that the lump is malignant. GPs recorded their impressions on a standard pro forma letter of referral, facilitating the allocation of appointments on the basis of urgency. Clinician education was enhanced as the outcomes were fed back. I recommend that those responsible for the organization of such clinics consider expanding the approach described by Roche *et al.* in this way.

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Letter 2

Sir

We welcome the paper by Roche *et al.* on the assessment of a scoring system for breast imaging. With increased pressure to standardize practice this is a timely and useful addition to the management of symptomatic breast disease. An objective imaging scoring system will be helpful in the formulation of clinical protocols and will facilitate the comparison of practice between breast units. However, we draw attention to a number of points regarding the management of patients with intermediate (C3) cytology.

C3 cytology is defined as showing all the features of benign aspirates with some degree of cellular atypia. We have recently reported our experience of the management of patients with a C3 diagnosis and a palpable breast lump[1]. Inevitably, an intermediate or equivocal cytological diagnosis will be relatively uncommon (6·4 per cent of all breast cytological reports over the 3-year period in our unit). It is suggested that the percentage of these that will ultimately be malignant to be in the range of 21–57 per cent[2]. In the present study the positive predictive value was 25 per cent and in our own study 21 per cent. A C3 diagnosis therefore carries a significant risk of underlying malignancy. In the present study all patients with a C3 cytology result and a benign imaging score ultimately had benign pathology. This led the authors to state that 'in lesions with atypical C3 cytology... associated with benign imaging if a patient does not wish surgery and the lesion is benign conservative treatment is safe, providing follow-up is adequate'. We feel a conservative approach carries some risks.

In our study 43 patients with a palpable lump had a C3 cytological diagnosis. All underwent objective clinical and radiological assessment at the time of presentation. In 37 patients definitive histology was obtained. This was benign in 26 but eight had an underlying invasive carcinoma, two had a phylloides tumour and one had a multifocal ductal carcinoma *in situ*. All but two of the patients with invasive malignancy had suspicious or frankly malignant imaging and/or clinical assessments. In the remaining two, however, both the clinical and radiological assessment was benign. One patient aged 72 years had a 5-mm grade 3 tumour and one aged 26 years had a 15-mm grade 3 tumour (benign on ultrasonography). We note that in the present study of the five tumours in patients under 35 years one was benign using the objective ultrasonography scoring system.

In conclusion we urge that lesions yielding C3 cytology be treated with caution. Intermediate cytology is often associated with underlying malignancy. The lesions most likely to be missed are small poorly differentiated tumours and those under 35 years who are imaged with ultrasonography. We recommend that definitive histology be obtained from all such lumps either by excision biopsy or core sampling.

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Book reviews

Clinical Cases for the MRCS and AFRCS

G. J. Morris-Stiff, D. J. Bowrey, M. C. A. Puntis, B. I. Rees and A. A. Shandall. 245 × 189 mm. Pp. 192. Illustrated. 1998. London: Arnold. £29.99.

With the advent of the MRCS has come a spate of new books filling this niche in the market. Having just passed my examination, I read this volume with an idea of what I was expecting from a book aimed at perifellowship candidates and a knowledge of what you need to know to pass. It is well set out, with 11 chapters addressing all subspecialties in the syllabus. The majority of the 142 cases, each covering a different topic, are illustrated with excellent photographs and radiological images. I particularly liked the intraoperative picture of a Meckel's diverticulum and the array of both paediatric and adult neck lumps. The reader's knowledge is then tested by five questions and the expected answer given in the answer section.

My main criticism is that the level at which some of the answers are pitched is higher than expected, for example the variable management in each of Neer's classifications of surgical neck and humerus fractures. The authors are somewhat pedantic in their management but understandably so to maintain brevity.

I recommend this book to examination candidates for visual aid and topic testing; I have had difficulty keeping it out of the hands of my colleagues long enough to read it.

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Hernias and Surgery of the Abdominal Wall. 2nd ed.

J. P. Chevrel (ed.). 277 × 195 mm. Pp. 340. Illustrated. 1998. Heidelberg: Springer. £84.

This is the English version of the second edition of *Chirurgie Des Parois de l'Abdomen*, a 340-page, hardcover book, divided into 12 chapters, translated from French into English by E. Goldstein and A. Marston. A multiauthor book under the direction of Jean-Paul Chevrel, five of the 14 first authors are from the North American continent and most are well known for their contributions to the rich hernia literature. The other authors are French, some also of great repute for their contributions to hernia surgery. Of the 451 illustrations, several photographs are unique historical documents; the drawings are very clear and instructive. As in the first edition, this book is divided into two parts. Within the first are three chapters, one dealing with the classical surgical anatomy of the abdominal wall with special emphasis on the anatomical weak spots that give rise to hernia; a second, unique for a book of this type, deals with the functional anatomy of the anterolateral abdominal wall; the third highlights two investigative procedures, ultrasonography and computed tomography.

The chapter on anatomy is certainly one of the most complete available and, as in the first edition, contains the essential but rarely cited (because hitherto untranslated into English) work of the French surgeon and anatomist Fruchaud, who introduced the notion of the myopectineal orifice. Once again, unfortunately, this work is not cited. The second chapter summarizes excellent data on the functional aspects of the abdominal wall, including electro and histoenzymopathological aspects. Although much is personal data relating to unreferenced studies, conspicuously missing is a discussion of the pathophysiology of the abdominal compartment syndrome and the all-important role played by the abdominal wall in its release. The only reference to this aspect of pathophysiology is in the (small) chapter on laparostomy, but this does not treat the subject adequately. The third chapter deals with diagnostic procedures. The modesty and honesty of the introductory remarks to the part on ultrasonography are to be commended.

The second part of this book relates to surgical techniques. The fruit of French research and thinking on the daily problems of inguinal and abdominal wall hernia repair are displayed. Several original ideas and operations are presented, some of which have not been published in English before. Among the authoritative chapters is that of René Stoppa, well known for his enthusiasm for and contributions about prosthetic mesh.

On the negative side, however, many ideas in this book are repeated from one chapter to another. Several of the references are quite old. A critical review of the classical as well as the laparoscopic techniques of inguinal hernia repair would have been a timely and interesting contribution, as several randomized studies are currently available that deal with both types of repair; the advantages of the laparoscopic techniques still remain to be defined. Missing are chapters on two specific and very difficult problems that should be in a book such as this: colostomy hernia and perineal hernia after abdominoperineal resection. All in all, this volume is unique in that it covers the classical as well as the less frequent problems pertaining to the abdominal wall. As such, it certainly deserves a place on the bookshelf of all surgeons interested in hernia and abdominal wall surgery.

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Crucial Controversies in Surgery 1998

M. Schein and L. Wise (eds). 245 × 174 mm. Pp. 274. Illustrated. 1998. Basel: Karger Landes Systems. Price not supplied.

This is the second volume in a series which the editors hope will be published annually. Despite the somewhat over-hyped title, it does succeed in highlighting areas both of current controversy and in which consensus is emerging. Each of the 15 chapters deals with a single surgical topic and comprises one (or occasionally two) commissioned articles, an invited commentary and an editorial comment. This fail-safe arrangement generally ensures good coverage of each topic, although the editors occasionally find themselves having to raise important issues that have been omitted from the main part of the chapter. The authors are predominantly but not exclusively from the USA, and the quality of their essays ranges from the brilliant (Vaidya and Baum on breast cancer) to the frankly poor (Yeo and Cameron on pancreatic cancer). Most are interesting and sound and offer up-to-date guidance for the practising surgeon.

The topics covered in the book's 15 chapters include not only gastrointestinal, breast, vascular and thyroid surgery, but also nutrition, organ failure, trauma and burns. Not all of these subjects will be of interest to every general surgeon but most will. The book's range, conception and focus are likely to make it particularly useful to those approaching the UK intercollegiate examination in general surgery.

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Scientific Surgery

The British Journal of Surgery is committed to practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English language publications. The full list of all these papers will be available in the Scientific Surgery Archive which will be held on *The British Journal of Surgery* website together with links to free Medline sites where abstracts can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Randomized trials

Charbonnier BA, Fiessinger J-N, Banga JD, Wenzel E, d'Azemar P, Sagnard L on behalf of the FRAXODI Group. Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis.
Thromb Haemostas 1998; 79: 897–901.
In a study of 651 patients with proximal deep vein thrombosis, the once daily regimen resulted in significantly fewer recurrent thromboembolic events (4·1 *versus* 7·2 per cent), haemorrhagic complications were similar.

Salmon RJ, Ansquer Y, Asselain B. Preservation *versus* section of intercostal–brachial nerve (IBN) in axillary dissection for breast cancer – a prospective randomized trial.
Eur J Surg Oncol 1998; 24: 158–61.
Preservation had no value in this study of 128 patients; shoulder function and sensation were similar. Preservation did not compromise surgical clearance.

McDonald M, Grabsch E, Marshall C, Forbes A. Single *versus* multiple dose antimicrobial prophylaxis for major surgery: a systematic review.
Aust N Z J Surg 1998; 68: 388–96.
A total of 28 randomized trials were analysed There was no significant advantage detected for multiple antibiotic doses. The authors ask why so many surgeons still employ them.

CLIP Group (Cancer of the Liver Italian Programme). Tamoxifen in the treatment of hepatocellular carcinoma – a randomized controlled trial.
Lancet 1998; 352: 17–20.
No advantage was detected in this multicentre study including 496 patients: median survival was 15 *versus* 16 months in controls

Ihlberg L, Luther M, Tierala E, Lepantalo M. The utility of duplex scanning in infrainguinal vein graft surveillance: results from a randomised controlled study.
Eur J Vasc Endovasc Surg 1998; 16: 19–27.
One hundred and fifty-two grafts patent 1 month after insertion were randomized to duplex or ankle-pressure follow-up. One-year secondary patency and amputation rates were similar – 84 and 88 per cent for ankle pressure, 71 and 81 per cent for duplex respectively.

Cheek CM, Black NA, Devlin HB, Kingsnorth AN, Taylor RS, Watkin DFL. Groin hernia surgery: a systematic review.
Ann R Coll Surg Engl 1998; 80 (Suppl I): S1–80.
A grand review of randomized and non-randomized studies with surprisingly few hard conclusions.

Verne JECW, Aubrey R, Love SB, Talbot IC, Northover JMA. Population based randomised study of uptake and yield of screening by flexible sigmoidoscopy compared with screening by faecal occult blood testing.
BMJ 1998; 317: 182–5.
Some 3744 patients were randomly offered faecal occult blood testing, sigmoidoscopy or both. Uptake of sigmoidoscopy was significantly higher than occult blood testing and was increased to 62 per cent by a telephone reminder

Wellwood J, Sculpher MJ, Stoker D, Nicholls GJ, Geddes C, Whitehead A *et al.* Randomised controlled trial of laparoscopic *versus* open mesh repair for inguinal hernia: outcome and cost.
BMJ 1998; 317: 103–10.
Of 403 patients randomized, laparoscopic repair was less likely to be done as a day case (89 *versus* 96 per cent), was less painful 2 and 3 weeks after surgery and the patients were more likely to be satisfied after 1 and 3 months It cost almost double.

Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C *et al.* on behalf of the Italian Tamoxifen Prevention Study. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women.
Lancet 1998; 352: 93–7.
Some 5408 women were randomized. After a median follow-up of 46 months a similar number of cancers was detected in each group: tamoxifen 19, placebo 22.

Powles T, Eeles R, Ashley S, Easton D, Chang J, Dowsett M *et al.* Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial.
Lancet 1998; 352: 98–101.
Some 2494 healthy women with a family history were randomized After a median follow-up of 70 months the frequency of breast cancer was similar: tamoxifen 34, placebo 36: relative risk 1·06.

The British Journal of Surgery website can be found at: http://www.bjs.co.uk. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about our website, either in writing or through the website address.

Instructions to authors

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Send four copies of original articles and other editorial matter to: The Editor, *The British Journal of Surgery*, Blackwell Science Ltd, 25 John Street, London WC1N 2BL, UK. Telephone: 0171 404 1831. Facsimile: 0171 404 1927. Books for review should be sent to the same address.

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Following final approval of articles, you will be asked to submit the accepted version on disk. These should be IBM-compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, software, and disk system if known. Do not justify. Please send us digital versions of your figures. Ideally, these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Avoid using tints if possible; if they are essential, try to make them coarse. Further details can be obtained from the publisher. Disks will not be returned to authors.

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The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethics committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs that might identify an individual. Submit evidence of such consent with the manuscript.

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The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts, which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* 1997; 336: 309–15, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, state in parentheses the brief name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal believes that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission signed leading articles which are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

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The Editors welcome topical correspondence relating to articles published in the Journal. Letters should not exceed 250 words and should be typed double-spaced.

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Title page

On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review etc.).

Abstract

This should be not more than 200 words on the second page of the manuscript and be presented in a structured format. **Background:** state why the study was done, and its main aim; **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings of the study; include important numerical values. **Conclusion:** state the main conclusion drawn from the results. Controversial or unexpected observations may be highlighted, but keep this section brief. Write the abstract in clear prose.

Tables and illustrations

Submit four copies of all illustrations and tables. Type each table on a separate page with an appropriate brief title. Line drawings are acceptable as clear black on white graphics, computer printout or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Include explanations of symbols and shading in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. If a table or an illustration has been reproduced from a published work give the original source in full. Obtain permission to use published work from the original author and the publisher before submission.

Abbreviations

Use abbreviations sparingly. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension by the reader. Use abbreviations consistently throughout the text and clearly define each one on first use.

Numbers and units

Use the decimal point, not a comma, e.g. 5·7. Use a space and not a comma after thousands and multiples thereof, e.g. 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, give the actual values and units, with SI equivalents inserted in parentheses at appropriate points.

Statistics

For detailed guidance on the handling of statistical material, consult *Br J Surg* 1991; 78: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; 276: 637–9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Do not use the '±' symbol; these statistics should be presented in parentheses after the mean value.

Analysis

Clearly describe which methods were used for which analyses; any methods not in common usage should be supported by references. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the P value, e.g. '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$'.

Actual P values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Do not confuse statistical significance with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

References

Type the references with double spacing in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged. Reference to unpublished communications will not be accepted. Cite personal communications in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, number the references consecutively by superscript: ^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; 66: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer, 1981: 123–63.

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